Experimental and statistical analyses of the effects of a uniform positive pressure applied to the lower limb in humans on vascular haemodynamics

by

Bérengère Michèle FROMY

Bsc, University of Glamorgan (1993)

Submitted to the School of Accounting and Mathematics in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

at the

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Abstract

The determination of required pressure level to provide an optimum treatment is an important task for vascular clinicians. This thesis is a first investigation including both venous and arterial femoral velocities and distal microcirculation of the forefoot to evaluate the effects of varying uniform external compression applied to the whole lower limb in humans.

The ultrasound technique has been used to evaluate the maximal venous and arterial velocities in femoral common vessels. The microcirculation and the cutaneous oxygenation of the forefoot were recorded by laser Doppler fluxmetry and transcutaneous oxygen and carbon dioxide pressure measurements respectively. The findings of the present investigation support the concept that a uniform pressure applied to the full length of a healthy leg when the subject is in recumbent position should probably not exceed 10 mmHg, since significant impairment of both macro and microcirculation can be found.

A database of information collected from twenty eight healthy subjects was established. Using this database and regression analysis, a new empirical model was produced which gave a hierarchical description of oxygen in terms of applied pressure and subject's characteristics. The developed model was expressed in terms of a cubic polynomial and was analysed in the content of catastrophy theory. This was appropriate to account for sudden changes in the data.

Although the results obtained were based on this preliminary study, it appears that the predictive results are extremely encouraging and form a solid basis for future research. The observations of cubic forms in medical statistics as well as the inclusion of micro and macro in a single model are approaches that have been neglected in the past. A further area of apparent neglect appears to be in the careful selection of the sampling intervals to optimise information content of the database.

Le choix du niveau de pression souhaité pour développer un effet optimal est une tâche importante pour les médecins vasculaires. Cette thèse est une première expérience comprenant les vitesses fémorales veineuses et artérielles, ainsi que la microcirculation distale du pied dans le but d'évaluer les effets d'une compression externe uniforme variable appliquée au membre inférieur chez l'homme.

La technique des ultrasons était préalablement utilisé pour la mesure des vitesses veineuses et artérielles maximales dans les vaisseaux communs fémoraux. La microcirculation et l'oxygénation cutanée du coup de pied étaient mesurées par laser Doppler et par mesure des pressions transcutanées d'oxygène et de dioxide de carbone respectivement. Les résultats de cette étude confortent l'idée qu'une pression uniforme appliquée à toute la jambe d'un sujet sain en position allongée (et sans doute encore plus chez l'artériopathe) ne devrait pas dépasser 10 mmHg. En effet, des perturbations significatives peuvent être trouvées en macro et microcirculation dès 10 mmHg.

Une base de données fut crée à partir de vingt-huit sujets sains. L'utilisation de cette base de données et l'analyse de régression ont permis le développement d'un nouveau modèle empirique. Celui-ci décrit l'oxygène en fonction de la pression appliquée et des caractéristiques du sujet suivant une structure hiérarchique. Le modèle développé est exprimé à l'aide d'un polynôme du troisième degré et fut analysé dans le contexte de la théorie des catastrophes. Cette dernière était appropriée pour reproduire les changements brutaux présents dans les données expérimentales.

Bien que les résultats obtenus soient basés sur cette étude préliminaire, ils sont très encourageants et forment une base solide pour de futures recherches. L'utilisation de termes du troisième degré en statistiques médicales, mais également l'introduction des aspects micro et macroscopiques dans un modèle unique, sont des approches qui semblent avoir été négligées dans le passé. Un autre aspect qui semblait être négligé dans les études précédentes, concerne le choix minutieux de l'échantillonage, afin d'optimiser l'information contenue dans la base de données.

Certification of Research

This is to certify that, except where specific reference is made, the work described in this thesis is the result of the candidate. Neither this thesis, nor any part of it, has been presented, or is currently submitted, in candidature for any degree at any other University.

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Candidate

Ron Wiltshire
Director of Studies

20 April 1998.
Date

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Chapter 1

INTRODUCTION

1.1 Aims and objectives

Since the beginning of mankind, the treatment of wounds has presented a challenge to those versed in the healing arts. In the case of venous insufficiency, the requirement for the application of compression bandages is generally accepted in the management of wound healing. However, the required pressure level and the method of its application to provide an optimum treatment is a delicate balance. Indeed the balance between the apparent beneficial effect on the venous system and the risk of arterial ischaemia resulting from an external uniform compression is unclear. Moreover due to aging of the population, there is an increasing prevalence to arterial disease. The diagnosis for the correct type of bandage and the variability of application of these bandages is not completely understood and there is an urgent requirement for a clinical analysis based system that will assist with the diagnosis of wound positions on patients and the repeatability of bandage pressures applied to the wound. In the United Kingdom, treatment of leg ulcers has been estimated to cost the NHS (National Health Service) about 600m pounds a year [56]. As the cost of sores in the community is huge, their prevention is a very important consideration in the nursing of patients. A model which is able to determine the required sub-bandage pressure would enhance bandage treatment and prevention strategy and hence, vastly reduce the cost spent on sore treatment and bandages each year. Therefore the aim of this study is to determine and evaluate the effects of a positive uniform compression applied to the lower limb on the haemodynamics and the distal microcirculation in humans. It is acknowledged that

in realistic treatment strategies, the compression may be graduated from ankle to groin. Such situations may be considered following this preliminary study.

1.2 Problem approach

The main aim of this thesis is to be met by means of two separate but linked analyses. In the first analysis an appropriate experiment is conducted so as to create a database allowing an experimental analysis. In the second analysis, a model, based on experiments, is devised to explain the relationship between externally applied compressive forces and resulting vascular effects in human lower limbs. The developed model is based on experimental observations collected throughout an investigation especially designed for the purpose. Included in the modelling strategy is the need to help the clinicians to choose the adequate pressure to apply to a patient according to his/her personal characteristics. These personal characteristics would make the model easy to use for a clinician.

To assist with these analyses it is necessary to review the physiological and anatomical processes governing circulation and microcirculation in humans for the development of a realistic model.

In addition, a literature survey covering aspects of current experiments and modelling related to the vascular haemodynamics in humans is essential. The aim of the literature survey is to look for experiments conducted under similar conditions which could be useful to design the experimental protocol. There were also other reasons for the literature survey. In rare cases when the data has been obtained under identical conditions to the present experiments, they could be used to enhance the database and so improve the efficiency of the model. The literature survey also covers different mathematical modelling approaches (such as physical models, black box models, statistical models). A model which contains stochastic variables must, by definition, be concerned with mathematical techniques appropriate to probability and statistics; deterministic variables call for the use of calculus. Therefore with respect to the modelling, it is necessary to understand mathematics based on partial differential equations, special functions, statistical methods, time series analysis, biophysics, but also fluids mechanics. Because of the complexity and variability of human characteristics, the assessment of the model

related to external pressure application on the lower limb could be developed via empirical analysis and modelling of data from experiments. The latter is the subject of this thesis in which all the experiments have been conducted in Angers University Hospital, France. The physical interpretation of models and their relationship with existing descriptions of blood flow are discussed later.

The wide range of mathematical applications can be illustrated from books on different mathematical disciplines, in particular "Mathematical Biology" by Smith [100]; a number of more general articles on modelling itself underline the general principles by Ford [24] and Wallis [111]. The models described in the literature fall generally into the following categories:

- Physical models
- Biological and medical models
- Statistical models
- Operational research methods

The mathematical part of the thesis has been developed at the University of Glamorgan, Wales.

1.3 Summary of the experimental approach

The external compression on the lower extremities, mostly realised by elastic compression, is used to prevent or to limit the oedema formation of various origin: chronic venous insufficiency, cardiac insufficiency, lymphatic alterations are mainly considered. It has been shown that a direct inverse relationship exists between skin blood flow and local applied pressure by Schubert [89] and Colin [18]. Moreover an inverse relationship between transcutaneous oxygen pressure (tcpO2) and external pressure has been found, although controversy exists whether it is linear or parabolic, Newson [71] and Seiler [91]. In attempting to find an explanation for the apparent beneficial effect of compression on venous function suggested as resulting from an improvement in calf muscle pump function with an increase in venous flow velocity or a reduction in venous reflux, studies have focused attention on the flow of blood in the deep or superficial venous system of the lower limbs; Sarin [84], Sigel [96].

A local external applied pressure as low as 40 mmHg produces a significant decrease upon transcutaneous oxygen tension and even a compression of 20 mmHg can decrease significantly the skin blood flow, as it was shown by Colin [18]. As the level of applied pressure in both studies varied in the same range, the balance between the beneficial effect on the venous circulation and the risk of tissue ischaemia due to an external uniform compression is still to be evaluated. Because of the controversy on the subject, an experimental protocol especially designed for the purpose of this study has to be performed. Its aim is to determine the effects of a positive uniform compression applied to the whole lower limb on both circulation and distal cutaneous microcirculation until a critical threshold was reached. The collected data are both femoral arterial and venous blood velocities (reflecting the circulation of the lower limb) and the transcutaneous oxygen pressure, the transcutaneous carbon dioxide and the laser Doppler flow signals on the forefoot (reflecting the distal microcirculation). Since a research team in the University Hospital of Angers, France, works on venous circulation in particular and has substantial expertise in experimentation designed to investigate vein function in detail, the experiments have been conducted in the hospital mentioned above.

1.4 Summary of the modelling approach

It is well known that mathematical models play an important role for scientists as they seek to further our understanding of nature.

Formulating problems in mathematical terms has several stages. First, it requires that premises are clearly stated. Real world problems are often complex, involving several different and possibly interrelated processes, especially in the biological applications. In the empirical fashion and before mathematical treatment can proceed, one must determine which variables represent the components of an implicit or/and explicit function that is expected to explain the process of interest. In the case of explicit expression, the variables that are central to explaining the process are noted as the dependent variables and all the other variables that significantly help explaining the dependent variables are called the explanatory or the independent variables. Often, for the relevant variables, relationships (e.g. a differential equation) are postulated in the form of laws, formulas, theories, etc.

The description deterministic model is usually used in cases where the outcome is a direct consequence of the initial conditions of the problem. This directness is not affected by any arbitrary external factors or, in particular, random factors. This approach frequently requires the use of differential calculus.

The term stochastic model, on the other hand, is reserved for those situations where a random effect plays a central role in the problem investigation. Many models of this kind are essentially "next-event" models often involving queues and services. Random arrivals at bus queues or random service times at the supermarket are common events for everyone. In these situations, the outcome is not fixed in the sense that it is unique because we have to allow for the random variability of arrivals and departures.

To sum-up, it is often useful to divide our mathematical models into two categories, deterministic and stochastic, but care is necessary because there are many situations where, within the same model, some features are random and others deterministic.

1.5 The organisation of the thesis

In Chapter 2, a review of the literature is given. Chapter 3 is an overview of the physiological knowledge of human circulation and microcirculation.

Chapter 4 contains a complete description of the experiment protocol conducted in Angers hospital. The results provided by the experiments are also presented in this Chapter.

In Chapter 5, the statistical model development is presented in detail.

The core body of the thesis is then ended with the conclusions, Chapter 6.

The Appendixes A to D contain the documents that were actively useful for the conception and the realisation of the experiments. As the experiments was conducted in a French hospital, these appendixes are written in French. In appendix E, the article accepted in Cardiovascular Research is presented. Some basic review of statistics are summarised in appendix F. The basis of the catastrophe theory is summarised in appendix G.

Chapter 2

LITERATURE REVIEW

The literature review covers the important aspects of other work done in the field of compression effects. Its classical importance have lead other researchers to investigate similar cases. Research in this area can be grouped into two main categories. Firstly, literature that details the medical and clinical background and rationale for the work is documented about the venous system. Secondly, literature concerned with the arterial system, particularly the mathematical models using different approaches, is reported. The information about cutaneous microcirculation is presented in Section 2.3.

There are many excellent books on the physiology and anatomy of the systemic circulation, such as Tartora [105], and aspects of these elements will be discussed in the following chapter. The physical principles that apply to the motion of blood through the vascular system are derived from the general laws of hydrodynamics, with certain modifications imposed by the properties of blood and the vascular tree. In the study of haemodynamics, it is natural to begin with the laws that govern the flow of simple liquids through a rigid cylindrical tube, since they are the foundation for the more elaborate laws needed to describe the flow of blood through the branching, distensible network of tubes that makes up the cardiovascular system. Therefore the study of the mechanics of blood flow in veins has been far less extensive than that of blood flow in arteries. To compensate for this lack, many clinical experiments have been performed to understand the mode of action of the veins under different conditions.

2.1 Venous system

Since deep venous thrombosis (DVT) and pulmonary embolism (PE) are significant causes of morbidity and mortality in ambulatory and moreover hospitalised patients, numerous techniques are used such as intraoperative electrical calf muscle stimulation, intermittent pneumatic compression by Nicolaides *et al.* [72], use of pharmacologically active agents by Torngren [109]. Frequently associated to those methods, the common used method of DVT prophylaxis, and the subject of the present study, is the use of external compression to reduce venous stasis and increase blood flow.

Largely reported in the literature, Pierre Dionis recommended to the Queen of France in the 17th century the use of rigid lace-up stockings made from coarse linen or dog skin to apply compression as it is reported by Meyerowitz *et al.* [67]. It was not until 1949, however, that using radiographic techniques showed that compression would increase venous flow velocity in the deep veins of the leg, Stanton *et al.* [102]. He concluded from his study that 20 mmHg was probably near the optimum for maximum acceleratory effect, due to a decrease in the cross-sectional area of the venous bed. In 1960, Meyerowitz *et al.* [66] showed that a stocking, which was claimed to exert 10 mmHg pressure at the calf, increased the rate of blood flow by an average of 160% in the stockinged limb in 28 of the 31 participants (one leg was subjected to compression, the other uncompressed was used as control). One patient had the same rate of flow in both limbs, and only two (6.5%) had a greater flow in the control limb. Venous flow rates in the leg were measured by means of ^{132}I-albumin. Four years later, Meyerowitz *et al.* [67] repeated the previous study using another technique (orthoiodo-hippuric acid tagged with ^{131}I). This time, they found a mean increase in blood velocity of 79% in 21 patients, no change in velocity with compression in 3 patients, and a reduction in velocity in 4 patients. On the other hand, Sabri *et al.* [83] suggested later that compression of the calf at a pressure of 10 mmHg produces complete collapse of the thin walled soleal sinuses. Overall in this study, 80% of patients showed an increase in blood velocity with compression but 20% showed no change. Inflatable splints were used in both animal and human to determine the effect of external compression upon "blood volume flow" through the leg, Sabri *et al.* [83], Spiro *et al.* [101].The results were very variable, but appeared to indicate that full length splints inflated to a pressure of 5 mmHg increased femoral vein flow by an average of 15%. At higher pressure, this initial

increase was progressively reduced until at 20 mmHg all limbs showed a reduction in blood flow compared with resting levels. As a result of their observations, Spiro *et al.* [101] concluded that the application of excess pressure, although reducing stasis may tend to substitute for it, a condition where the vessels are empty and collapsed, and they suggested that this in fact could increase the chance of thrombosis when blood flow is restored by causing intimal damage during the period of collapse. Chant [17] suggested that the transient rise in femoral blood flow was due to the emptying of the veins by compression, and the removal of tissue fluid by pressure. In 1973, Sigel *et al.* [96] criticised the use of single chambered compression sleeves, as they tend to hold the leg in full extension producing a functional obstruction to blood flow in the popliteal vein. They determined the effect of stocking induced compression and body tilt position on deep venous blood flow velocity in 10 volunteers using a non-invasive Doppler ultrasound technique. In a second study, Sigel *et al.* [97] attempted to determine optimal compression to reduce venous stasis in terms of the amount and manner of application (graded or uniform). Uniform compression produced a 10% increase in velocity compared with 36% produced by the graduated 18-8 mmHg pressure profile. Further evidence for the value of the compression profile identified by Sigel was provided by Lawrence and Kakkar [53]. Many other studies were conducted in the clinical use of static compression in the prevention of deep vein thrombosis: Wilkins *et al.* [114], Scurr *et al.* [90], Torngren [109], Hansberry *et al.* [34]; or the use of stockings in orthopaedic surgery: Ishak *et al.* [41].

2.2 Arterial system

Numerous models have been published to define the flow in arteries. The first type of models study the arteries as simple and well-defined geometric tubes. In this case, hydraulic and mechanic equations are used, and their solutions are solved while the simplifications are limited to keep the model as realistic as possible. In the simplest models, analytical analyses are widely suggested; whereas numerical techniques are used when the model is more complex. In most cases, the blood is supposed to be a homogeneous fluid, considering the arteries to be large vessels compared to the size of red cells. It is unanimously accepted that the blood is incompressible, and that the flow is laminar in absence of stenosis or bifurcation. The Hagen-

Poiseuille model (19th Century) is the first model, and became the basis of more sophisticated models. A Newtonian fluid studied in rigid tube led to a stationary flow, where the velocity diagram in the cross-sectional view is parabolic.

On the other hand, a few authors studied the ideal arterial branching of the cardiovascular tree: Murray [70], Kamiya *et al.* [47], Zamir [121]. In 1981, Fung [30] proposed solutions for the Hagen-Poiseuille problem including different rheological characteristics for the blood. Then the rigid conduct has been replaced by an elastic tube with a thin wall responding to linear elastic behaviour by Rashevsky [80], Morgan [69]. The results from these analyses led to parabolic distribution of the velocities. In 1984, Fung [31] used similar methods to establish a linear radius-pressure relationship. Original works studied a pulsatile flow in a rigid tube: Schlichting [88], McDonald [62].

The mathematical treatment by Franck [25] is a landmark in the history of haemodynamics, although he treated the arteries as a single chamber in accordance with the Windkessel model, and the transmission of pressure and flow waves along the arteries was consequently not included in his original work. Some researchers abandoned the Windkessel concept: Bergel [8], McDonald [63], Noordergraaff [74], Taylor [106], Womersley [115]. McDonald [63] used a real pressure curve over a full cardiac cycle in an artery to predict a velocity curve very close to the reality. However the amplitudes differ from those measured on some occasions. These differences could be due to the assumption that the artery was a rigid tube (allowing no propagation waves in large vessels). Therefore some authors proposed a model with deformable walls. Georges Riemann (1826-1866) presented the link that exists between the wall distensibility and the waves propagation velocity. Similarly is the famous JR Womersley model, 1955: the tube is elastic and thin, and contains a Newtonian fluid. The resulting equations were linearised and solved using the principle of superposition. The solution led to two different types of transmission: the first concerned the transversal waves, whereas the second concerned shear forces in the artery. Results using this type of model appeared interesting but a large part of variability was not explained. To minimise these errors, researchers have tried to improve Womersley's approach: Ling *et al.* [55] used a non-linear model, Fung [31] used a model with an anisotropic and visco-elastic wall, Mirsky [68] used a model with a fixed thickness wall, Klip [50] used asymmetric flow analysis, Kaimal [46] used the effect of the frequency on the viscosity

of the fluid. To extent these model approaches to more than one tube appeared to be very difficult because formulation of the flow behaviour in an artery was uncertain. Methods based on characterisations of some aspects of the phenomena (using simpler equations) have therefore been developed: classical electrical components (resistance, capacitance, inductance) are used in equivalence to the conducts network. In those cases, pressures are substituted by voltages, and flow rates by current: Avolio [7], Burattini *et al.* [13], Klabunde *et al.* [49], Jackman *et al.* [42]. Clearly such studies are restrictive and cannot be used to study the circulation as a whole. Such models are therefore called local models and may be used for bifurcations analyses for instance, Friedman *et al.* [27], Fenton *et al.* [23]. A nonlinear mathematical model of arterial blood flow, which can account for tapering, branching, and the presence of stenosed segments, is presented by Porenta *et al.* [78].Using the finite element method, the model equations are transformed into a system of algebraic equations which can be solved on a high-speed digital computer to yield values of pressure and volume rate of flow as functions of time and arterial position.

Since the arterial pressure is high, the effect of an external compression was mostly studied in arterioles presented in the next section.

2.3 Microcirculation

Although blood flow through a capillary segment is obviously a function of the pressure applied as a driving force and the viscous resistance of blood and the vascular tube, it is not possible to present a quantitative description of capillary resistance to flow similar to that of the larger vessels. The complex architecture of capillary networks, highlighted by Fung *et al.* [29] and Zweifach [122], makes physical analysis of pressure-flow relationships a difficult problem for both fluid dynamicists and physiologists. In his original paper, Skalak [99] studied three kinds of models of capillary blood flow. The blood cells are modelled using rigid cells of the usual biconcave shaped red blood cells, normal flexible red blood cells and viscoelastic spheres in a capillary. He showed that the "deformability of red blood cells is important in reducing the apparent viscosity in capillary blood flow".

Ashton [5] and Yamada [116] measured blood flow in man at raised applied external pres-

sures. However there appears to be relatively little information on regional blood flow in clinical conditions associated with raised tissue pressures, and even less for conditions of localised increased tissue pressure such as the compartmental syndromes. Ashton [6] concluded that theoretical consideration of the factors involved in maintaining vascular equilibrium and experimental evidence in man indicate that at high tissue pressures there may be a sharp decline in blood flow and, in certain situations, complete cessation of blood flow even at tissue pressures below mean arterial pressure. It seemed that at least two mechanisms are involved. Firstly, active closure of small arterioles under vasomotor tone when transmural pressure is lowered (either by falls in intravascular pressure or rises in tissue pressure). Secondly passive collapse of soft-walled capillaries when tissue pressure rises above intracapillary pressure. These mechanisms are likely to assume particular importance when tissues are surrounded by non-compliant fascia and may thus be involved in compartmental syndromes. Visualisation of the intramuscular microcirculation during and after compartmental syndrome was studied by microangiograms and histologic cross sections by Har-Shai *et al.* [35]. Since the quantitative relationship of intracompartmental pressure to the histology, blood flow, oxygenation and function of the involved musculature has remained unclear, Sheridan *et al.* [94] developed a model system in which the pressure within the anterior tibial compartment of a rabbit may be accurately controlled to study the effects of increased intracompartmental pressure on the physiology of muscle and nerve. Their investigations demonstrated that increased intracompartmental pressure alone, without other associated vascular injury, may produce muscle hypoxia and loss of neuromuscular function. The continuous monitoring of intracompartmental pressures may be useful clinical adjunct in the management of patients at risk for a compartmental syndrome. In spite of much research in this field, it appears that quite conflicting opinions exist regarding the principal mechanism(s) responsible for the deranged circulation during increased tissue pressure. To resolve this controversy, it is a need to examine in vivo observations in more details. This can provide simultaneous quantitative information about the pressure-flow relationships, the macro and microvascular adjustments and the capillary events occurring in an organ exposed to well-defined increases in tissue pressure. Shrier *et al.* [95] suggested that increases in pressure surrounding a muscle limit flow mostly through an increase in critical closing pressure and only through a small increase in arterial resistance. They supported the presence of an arteriolar

vascular waterfall in the skeletal muscle circulation. Mellander [64], [65] investigated several studies in this field and reached alternative conclusions. The hypotheses for the mechanism responsible for the deranged circulation during increased tissue pressure are still controversial.

2.4 Critical conclusions

Numerous mathematical models have been constructed to describe the human arterial blood flow as shown in Section 2.2. Many established models are based on unrealistic assumptions which need to be satisfied. This usually restricts the application of the model to particular scenarios.

In some cases the physical processes are simulated directly while in others it is the overall effect of the physical processes which is simulated. In either event, the modeller will be required not only to solve the model equations but also to provide appropriate values for the coefficients in those equations. In the ideal world such coefficients would be measurable physical quantities such as bone density, living tissues properties, but in practice they are often quantities which are either poorly defined in physical terms or are difficult to measure, e.g. mixing coefficients or almost all human coefficients. In addition, because natural vessels are longitudinally non-uniform (particularly in the venous and capillary systems), the modeller does not just require a single value for each coefficient, but requires their spatial distribution: in unsteady flow applications, the temporal variation of the coefficients is needed also.

It is evident that the fundamental principles and the general equations are applicable to all fluids, and in order to adapt them to specific numerical cases all that is necessary is a knowledge of the values of certain physical properties such as viscosity and density. Fluid mechanics is the science of the mechanics of liquids and gases and is based upon the same fundamental principles as are employed in the mechanics of solids. It deals with both compressible and incompressible fluids, or, in other words, with fluids of either variable or constant density. However, in cases where there is an appreciable change in specific volume, thermodynamics has also to be involved.

Analytical solutions for three-dimensional problems are quite difficult to obtain, and the number of problems which have been solved in an exact fashion to date is surprisingly small.

Chapter 3

PHYSIOLOGICAL REVIEW

3.1 Introduction

Following from the main aims of the study, relevant knowledge of anatomical and physiological processes of human circulation are important to achieve a realistic model. It is essential at this stage to understand the basis of the blood mechanisms in the lower limbs, as well as the anatomical architecture of the entire network of arteries, capillaries and veins. The objective is to review information about the human circulation and microcirculation, in the systemic system. This includes the anatomy of the systemic vessels and the general mechanical processes of the circulation. Physiology and pathophysiology are also presented in this chapter. It ends with a discussion of the different existing types of bandages and stockings; covering compression classification.

In particular, pulmonary circulation and its vessels will not be developed in this chapter. The pulmonary circulation conveys the overall output of the right ventricle via the pulmonary arteries to the alveolar capillaries and returns the blood, via the pulmonary veins, to the left atrium. The pulmonary system is a low pressure and low resistance system compared to the systemic system which is developed below.

3.2 Anatomy of the systemic vessels

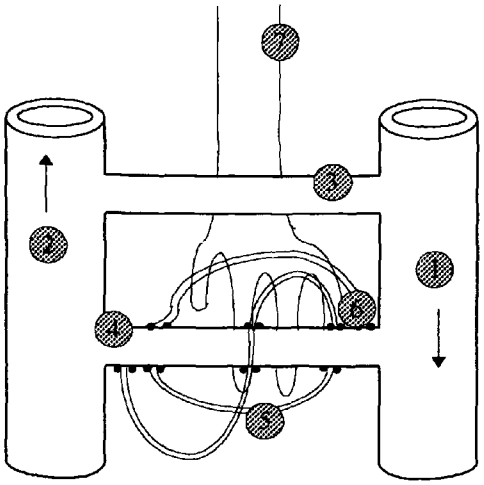
The human blood vessels form a closed system of conduits which can be divided into three main types: arteries, capillaries and veins. These conduits carry blood from the heart to the tissues and back to the heart. The following sections describe briefly the distinct vessels in the systemic circulation only. It can be noted that depending on their site (muscle, skin, splanchnic system), the properties of the vessels may clearly differ from one to another. Therefore the following description of the vessels is restricted to a general presentation of their properties in the lower limbs.

3.2.1 Arteries

The systemic arteries carry the blood from the left ventricle of the heart to all parts of the body. Since the blood within them is under high pressure, their walls are necessarily thick and strong (Laplace's law). The arterial system has a much lower capacity than the venous system. Firstly because the number of vessels is greater in the venous system than in the arterial system, and secondly, at a particular level, the veins draining a vascular bed tend to be larger than the corresponding arteries supplying it.

3.2.2 Capillaries and venules

After repeated divisions, the tiny artery (arteriole) breaks up into a group of tiny tubes. Such a vessel is called a capillary. The oxygen delivered to surrounding tissues cannot pass through the walls of arteries and veins, but it can pass through those of the capillaries which consist of one layer of intimal cells. Therefore the capillary flow rate assures the nourishment and the exchange between tissues. The transition from the capillary to vein is a gradual one (throughout the venules). The vascular bed lying between the arterioles and the venules is complex and variable in pattern (Figure 3-1) and includes not only the capillaries but also certain small vessels that differ from true capillaries in structure and function (see section "The mechanics of the circulation"). This whole network of microscopic arteriovenous pathways is known by the general term microcirculation. The anastomotic output drives the blood directly from the arteriole to the venule; it does not fulfill the nourishment role. Its main function is the thermal



1- Arteriole
2- Venule
3- Suquet canal
4- Preferential canal
5- Capillary
6- Pre capillary sphincter
7- Lymphatic canal

Figure 3-1: Schematic diagram of a microcircular unit (from Boccalon, 1997)

regulation of the skin.

With the venous system, the lymphatic system is the second backway towards the heart. It consists of two elements: the nodes and the lymphatic canals.

3.2.3 Veins

The veins are subdivided into two systems, superficial and deep, according to their relationship to the deep fascia. The systemic veins begin at the venules, where the capillaries join together, and end where the venae cavae enter the right atrium of the heart. Unlike arteries, the veins are equipped with valves to prevent pooling and backflow of blood into areas that they drain. The number of valves present in the different veins of the circulation increases towards the periphery of each limb to limit the effects of the gravity, the muscular contractions or thoracic hyperpressure.

Although regional differences are found in the venous system, this system fulfills one or more of the three following actions:

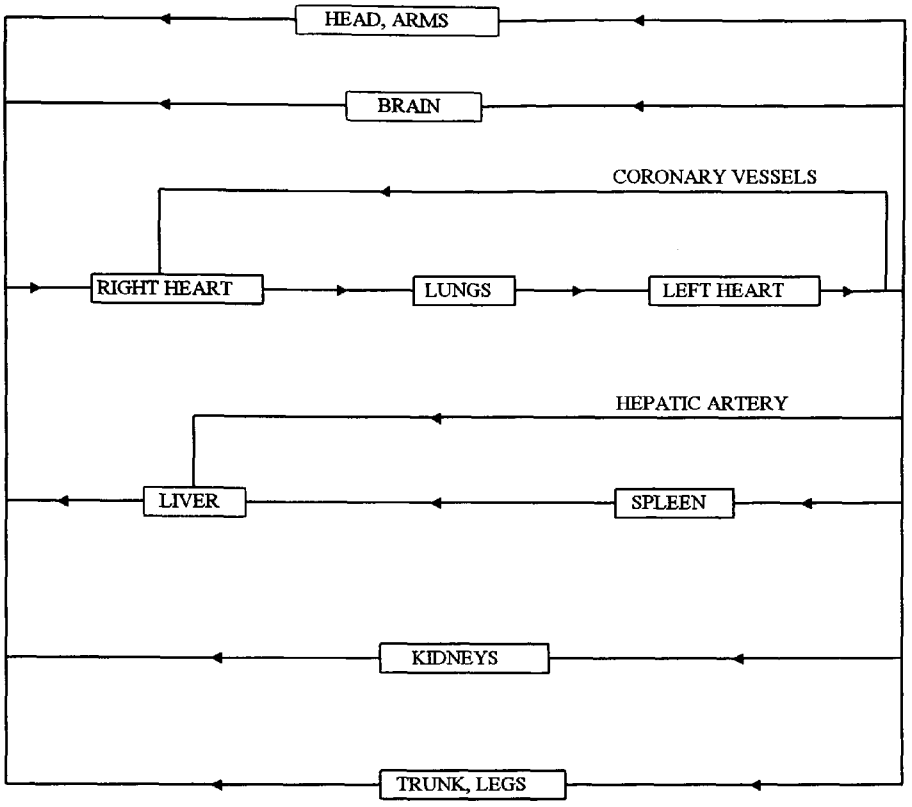


Figure 3-2: The parallel arrangement of organ blood supply to the upper and lower body. (Adapted from The Human Cardiovascular System, Facts and concepts, JT Shepherd and PM Vanhoutte, 1979, Raven Press, New York).

- the thermal regulation with the superficial system. This system takes part in thermal exchanges between the blood and the ambient air through the skin,
- the variable ability of the system due to the venous wall distensibility (about 100 times greater than the arterial one) and the large number of veins,
- the venous backflow to the heart due to muscular fibers and the venous tone.

3.3 The mechanics of the circulation

All the blood flows through the lungs. Inversely the systemic circulation is made up of numerous different circuits in parallel as it is shown in Figure 3-2.

This arrangement permits wide variations in regional blood flow without changing total systemic flow. Indeed the total volume of blood in the systemic circulation is constant over a short-term period of time. This volume is not uniformly divided between the pulmonary and systemic circulation, Tartora [105]. At any one time,

- about 80% of the blood that is in the systemic circulation is divided as follows:
  - 15% in the arteries
  - 5% in the capillaries
  - 60% in the veins
- and 20% of the blood that is in the pulmonary circulation is divided as follows:
  - 12% in the pulmonary vessels (almost equally divided between the pulmonary arteries and pulmonary veins)
  - 8% in the heart

Any change in volume in one part of the whole circulation leads to a reorganisation of the different circuits, and in particular a venous adaptation is performed because a large proportion of blood volume (compared to the total volume) is contained in the systemic veins.

Finally the circulatory system can be represented as a closed loop circulation system with two pumps (Figure 3-3). These two pumps allow the cardiac output (or total blood flow) to be variable. For instance the total cardiac output will increase due to exercise or hyperthermia. But the distribution of the cardiac output between skin, muscle and other major organs (such as heart, brain, kidneys, liver) will change in proportion in both situations. Figure 3-4 provides clues on how cardiac output might be distributed to organs.

3.3.1 The heart

The heart is a hollow muscular organ of a conical form, placed between the lungs, and enclosed in the cavity of the pericardium. During the diastole, the ventricle fills up, whereas during the systole (contraction), the blood is thrown away. These actions are repeated periodically at a frequency of 70-80 cycles per minute at rest (heart rate).

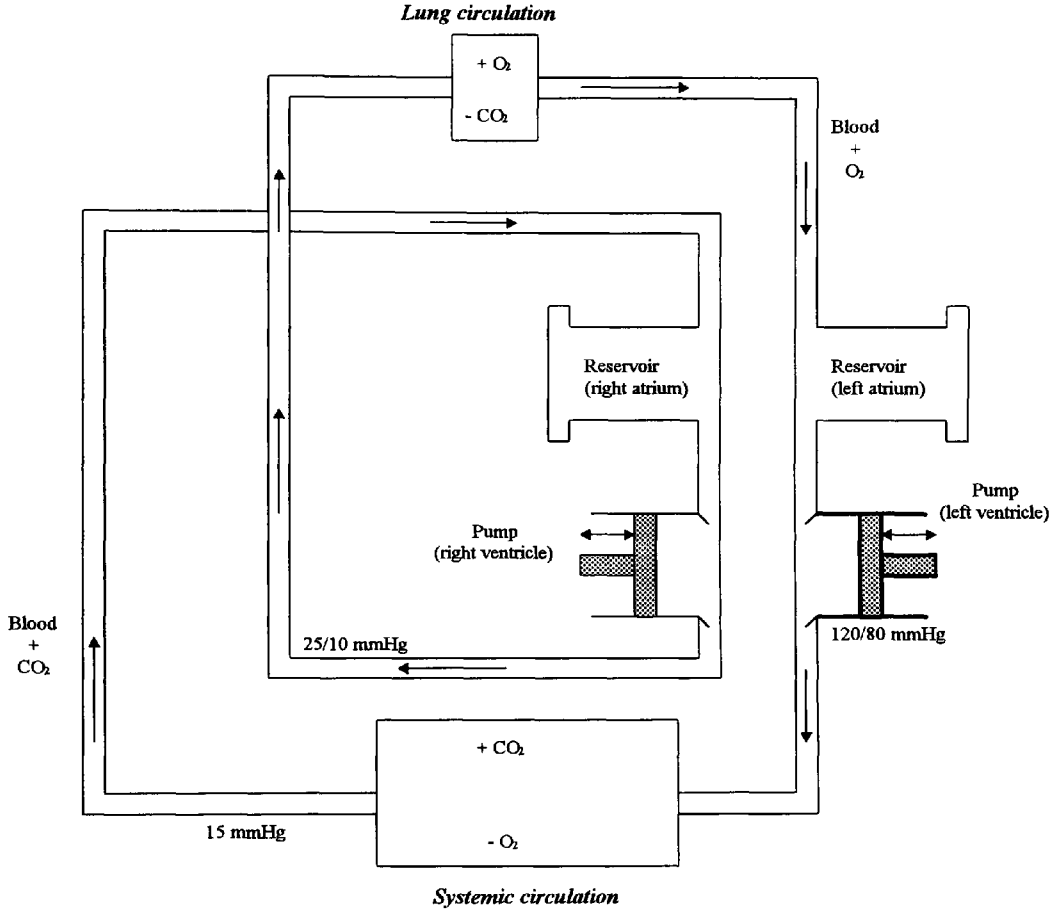


Figure 3-3: Schematic representation of the phasic or average pressure distribution within the systemic and pulmonary circulations in a normal, resting human adult in supine position (Redraw from Berne RM, Levy MN. Principles of physiology. Mosby-year-book Inc., Missouri 2nd edition 1996).

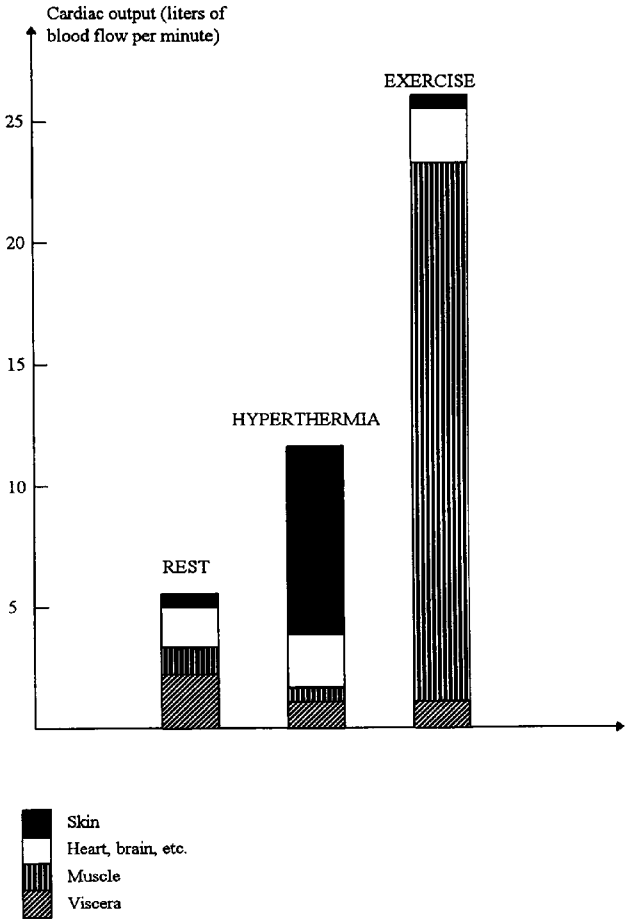


Figure 3-4: Total blood flow and its estimated distribution between major organs at rest, during severe hyperthermia (temperature greater than $39°C$) and during exercise. (Redraw from Rowell, 1986)

3.3.2 The peripheral heart

Active calf muscles, in their fascial envelope, act as a pump, forcing deep venous blood upwards towards the heart. The calf pump has been called the peripheral heart for the numerous similarities which they have in common. During the systole, when the calf muscle and the muscles in the deep posterior compartment of the lower leg contract they raise the pressure in and around all the structures contained within the deep fascia. As the intramuscular veins are completely compressed due to the pressure generated, the blood is squeezed out of the veins. The valves in the veins ensure that the blood flows only towards the heart. During the diastole, the pump chamber is refilled by the arterial inflow and the flow from the superficial compartment.

3.4 Physiology and pathophysiology

3.4.1 Arterial pathology

Arterial disease has many forms. It is subjected to many risk factors, and affects many different groups of people, particularly in the developed countries. It is becoming current practice for clinicians to evaluate the economic criteria of health care: Weinstein [112], Launois *et al.* [52], Hedges [37], Mancia [57], Van den Brand *et al.* [110], Simoons *et al.* [98], Roquebrune *et al.* [82], Elkan [20]. This evaluation has become more and more necessary, particularly in view of the increase of certain risk factors - for example, those linked to nutrition, sedentary life-style, stress, and an ageing population (which is now making its presence felt but will increase further beyond the year 2005). In view of the many different strategies used to manage vascular disorders and the costs involved in the disease, diagnosis, care, hospital admission, investigations, cessation of activity and treatment, some studies analyse the cost or cost/efficacy or cost/benefit relationships of preventive, diagnostic, or therapeutic strategies.

Peripheral occlusive arterial disease of the lower limbs is a common disorder; it is the local effect in the arteries of a systemic disease associated mainly with atherosclerosis. In industrialised countries it occurs in 1-5% of adults aged 30-64 years (source: summary of descriptive epidemiological studies of the prevalence of intermittent claudication based on diagnosis made from clinical examination and questionnaire). Indeed the prevalence of peripheral arterial dis-

ease increases with age whether assessed by symptoms of claudication or non-invasive testing: Hughson *et al.* [40], Reunanen *et al.* [81], Criqui *et al.* [19]. Elderly people with isolated systolic hypertension are at particularly high risk of atherosclerotic events and might be expected to have a high prevalence of atherosclerotic obstruction of the lower extremities. The prevalence of peripheral arterial disease has been shown to be dramatically underestimated by symptoms of intermittent claudication (IC). Lower extremity arterial disease is usually evaluated using the ratio of ankle-to-arm systolic blood pressure, commonly referred to as ankle arm index (AAI).

3.4.2 Venous pathology

Chronic venous insufficiency (CVI) is used to define any functional disturbances in the venous system. This disturbance of the venous system leads to valvular incompetency, consecutive or not to venous obstruction, in superficial or/and deep veins.

Chronically disturbed haemodynamics in the veins of the leg may be caused principally by primary varicose veins or by deep venous thrombosis. Valvular incompetence whatever its etiology allows retrograde pressure waves, which occur with each calf muscle contraction, to extend as far as the venules and the capillaries of the distal part of the lower leg.

Compression by means of bandages or stockings is widely accepted as standard treatment for CVI. Elastic support regulates venous flow by compressing the superficial vein lumen and supporting valvular function and the muscle pump, Partsch [76], Mayberry *et al.* [59]. It also reduces and prevents oedema, by reducing venous backflow, and by improving lymphatic transport. Even if an external compression has proved useful for venous disorders, this is only built on clinical observations and the exactness of the compression effects on the haemodynamics is not totally clear.

On the other hand, a compression represents a potential danger in arterial disorder cases. Moreover patients rarely have venous or arterial disorders separately. In most cases, when the venous system presents disorder, the arterial system is not perfectly healthy (and vice versa). Therefore the choice and the efficacy of the treatment always depends on the exactness of the diagnosis of the patient.

In recent years attention has been turned to the microcirculatory aspects of CVI. Cutaneous microangiopathy, e.g. changes in skin capillary morphology and reduced number of capillar-

ies/mm, has been described by Bollinger *et al.* [10], Haselback *et al.* [36], Leu *et al.* [54]. The nutritive component of cutaneous circulation is therefore severely impaired in the affected areas in patients suffering from CVI, Fagrell [22]. Capillaries dilate and elongate and become tortuous. Because of their glomerular shape the capillaries develop functional arteriovenous shunts which significantly reduce their transport capability, Junger *et al.* [45]. As trophical skin changes become more severe the number of capillaries diminishes drastically and extended blood flow stops reducing the number of nourishing capillaries, Franzeck *et al.* [26]. In the severe stage of the disease transcapillary diffusion increases and contributes to oedema. Because of the microangiopathy of the nutritional capillaries transcutaneous oxygen tension decreases in moderate and severe stages of CVI. Clinical hyperthermia of the congested skin, however, indicates hyperperfusion in most patients with more severe stages of the disease. Thus total blood flow to the skin is more likely to be increased, as proven by laser Doppler fluxmetry by Partsch [77] and positron emission tomography by Hopkins *et al.* [39].

3.4.3 Other diseases

Pathology of the microcirculation in the extremities

The acrosyndromes represent the overall painful syndromes of the extremities. They can be either vascular or non vascular. The vascular acrosyndromes may be caused by functional origin (paroxystic or permanent dystonic) or organic origin (dystrophic) due to parietal alterations of the vessels (microangiopathy). The non vascular acrosyndromes are neurologic acrosyndromes or cutaneous angiodysplasies. These types of acrosyndromes are beyond the scope of the present thesis.

The main physiopathologic factors of the vascular acrosyndromes are reported below:

- Sympatic hypertony: vasoconstrictor tonus is excited by cool stress, emotion. It is one part of the process leading to Raynaud disease.
- Haemodynamic factors: a low arterial pressure can decrease the microcirculatory output. Therefore Raynaud disease is associated to arterial hypopressure.
- Humoral factors (for example serotonine, histamine) are numerous and some more have to be discovered in the future.

Lymphatic pathology

Obstructive or mechanical lymphatic insufficiency are caracterised by a normal lymphatic load, whereas the ability of the lymphatic vessels to work is reduced. It is the case of lymphoedema which can be due to organic or functional disorders. Lymphatic insufficiency can also be caused by haemodynamic troubles. Disorder in the lymphatic system leads to liquid and immune imbalance.

3.5 Dressing and compression bandaging

Dressing materials are now available in a wide range of physical forms and with differing properties, Thomas [107]. It is important to have some idea of the strengths and weaknesses of the different types of dressings. A dressing may protect the wound from the external environment, retain moisture, absorb exudate blood and odour, provide a contact surface, influence perceived pain, support the wound. The bandages are particularly used in patients with poor mobility, as they are restricted in movement to promote the natural venous return through walking and other forms of exercise.

The following information is important to understand the further classification of the compression bandages, which should be applied to venous ulcers but never to patients with arterial problems. In the latter case a light bandage is applied only to secure dressings.

1. Extensibility of the bandage determines the change in length that is produced when the bandage is subjected to an extending force.

2. Power or modulus determines the force that is required to bring about a specific increase in bandage length.

3. Elasticity determines the ability of the bandage subjected to an extending force to resist any change and return to its original length once the applied force has been removed.

4. Compression implies the deliberate application of pressure to produce a desired clinical effect.

5. Support may be defined as the retention and control of tissue without the application of compression, and is usually provided to prevent the development of a deformity or a change in shape of a tissue mass due to swelling or sagging.

6. Conformability of a bandage determine its ability to follow the contours of the limb.

As mentioned earlier, it is possible to classify the compression bandages. They are commonly defined by three distinct types:

- Type 1: Lightweight conforming-stretch bandages: they are products which have a simple dressing retention function.

- Type 2: Light support bandages: they may be used to prevent the formation of oedema and give support in the management of mild sprains and strains (e.g. Crêpe).

- Type 3: Compression bandages are further subdivided into four groups:

  - Light compression bandages- 14-17 mmHg at the ankle (e.g. Elastocrêpe, Litepress).
  - Moderate compression bandages- 18-24 mmHg at the ankle (e.g. Tensopress, Veinopress, Setopress).
  - High compression bandages- 25-35 mmHg at the ankle (e.g. Tensopress, Veinopress, Setopress).
  - Extra high-performance compression bandages- pressures of up to 60 mmHg at the ankle (Blue Line, Elastoweb).

Stockings come in three ranges according to the degree of compression:

- Class I: 14-17 mmHg - suitable for mild varicose veins.
- Class II: 18-24 mmHg - suitable for prevention of recurrence of venous ulcers on small legs and slim patients and for mild oedema.
- Class III: 25-35 mmHg - suitable for chronic venous insufficiency and oedema, large heavy legs.

In venous ulcer management, the use of graduated compression, Lawrence *et al.* [53], from the base of the toes to the knee is justified by the need to reduce blood pressure in the superficial veins. This aids the blood to return to the heart by increasing the velocity of flow in the deep veins and finally reduces oedema by reducing the pressure difference between the capillaries and the tissues. Methods of achieving graduated compression include the application, to the lower limb, of:

- Bandages, e.g. Blue Line, Tensopress, Setopress, Veinopress, Elastocrêpe.
- Shaped elasticated tubular bandages, e.g. Tubigrid.
- Compression stockings, e.g. Venosan, Sigvaris, Jobst, Medi (UK).

Intermittent pneumatic compression therapy could also be used, Tarnay *et al.* [104]. In this case, the compression is controlled by an external pressure cycle on a limb using compressed air, which intermittently inflates a specially designed garment fitted to the limb.

Chapter 4

CLINICAL INVESTIGATION

4.1 Introduction

To meet the aim of the present thesis, an experiment was conducted in Angers University Hospital, France, (« Service d'Explorations Fonctionnelles Vasculaires ») with the collaboration of Prof. Jean-Louis SAUMET and his team. The experiment is fully detailed in a report which is presented in Appendix A. The experimental protocol was approved by the institutional review committee (CCPPRB standing for Comité Consultatif pour la Protection des Personnes dans la Recherche Biomédicale) of Angers on the 18th June 1996 and was conformed to the Huriet Law presented in Appendix B.

> Article L. 209-18 (Titre IV - Dispositions particulières aux recherches sans bénéfice individuel direct): « Les recherches biomédicales sans bénéfice individuel direct ne peuvent être réalisées que dans un lieu équipé des moyens matériels et techniques adaptés à la recherche et compatibles avec les impératifs de sécurité des personnes qui s'y prêtent, autorisé, à ce titre, par le ministre chargé de la santé. »

4.2 Inclusion - exclusion visit

4.2.1 Participants

The maximum number of subjects for this study is limited to 80 participants, classified into four groups. The groups are defined as follows:

- Group I Healthy young subjects (18-30 years old)
- Group II Healthy elderly subjects (50-70 years old)
- Group III Patients with a peripheral arterial occlusive disease of the lower limb (50-70 years old)
- Group IV Patients with a Chronic Venous Insufficiency CVI (50-70 years old)

The classification of the subjects was performed in order to observe the age effect, the state of the venous or arterial system effect in the relationship between the external applied pressure and the response of the femoral vessels velocities and the microcirculation of the forefoot.

4.2.2 Inclusion criteria

Common criteria

Subjects with the following characteristics were selected.

- Those of either sex, Caucasian and who were volunteers,
- Those who were able to understand the purpose of the experiment and its risks,
- Those who read and have signed written informed consents in duplicate,
- Those who did not reach the maximum annual amount of 25000 French Francs for therapeutic protocols (Huriet Law 88-1138 on 20/12/88, Article on 21/02/94),
- Those who belonged to the « sécurité sociale. » (French National Social Insurance)
- Those who had a normal electrocardiogram (ECG), a systolic arterial pressure (SAP) between 100 and 140 mmHg, a diastolic arterial pressure(DAP) between 50 and 95 mmHg.

Specific criteria for the inclusion of participants in group I

- Those who were between 18 and 30 years old,
- Those who had a normal clinical and vascular examinations,
- Those who had a normal ratio of ankle-to-arm systolic pressures (AAI) in both limbs ($1<AAI<1.2$), normal veins and arteries of abdominal and lower limbs examination by colour Duplex scanning.

Specific criteria for the inclusion of participants in group II

- Those who were between 50 and 70 years old,
- Those who had a normal clinical and vascular examinations,
- Those who had a normal ratio of ankle-to-arm systolic pressures in both limbs ($1<AAI<1.2$), normal veins and arteries of abdominal and lower limbs examination by colour Duplex scanning.

Specific criteria for the inclusion of participants in group III

- Those who were between 50 and 70 years old,
- Those who had a ratio of ankle-to-arm systolic pressures in both limbs less than 0.9,
- Those who had a vascular examination by colour Duplex scanning showing up an arterial lesion.

Specific criteria for the inclusion of participants in group IV

- Those who were between 50 and 70 years old,
- Those who had a normal ankle to brachial systolic pressures ratio in both limbs ($1<AAI<1.2$),
- Those who had a clinical and vascular examination showing the CVI but normal arteries of abdominal and lower limbs. The latter being examined by colour Duplex scanning considering the age of the participant.

4.2.3 Exclusion criteria

Subjects with the following characteristics were not selected for the present study:

- Those younger than 18 years old, aged between 30 and 50, older than 70,
- Those who gave no written informed consent,
- Those who had psychological or comprehension difficulties to understand the protocol,
- Those who had a pathological disease other than peripheral arterial occlusive disease and CVI (groups III et IV),
- Those who had an activity which could exert a large influence on the physiological state of the vascular system,
- Those who had a peripheral arterial occlusive disease of the lower limbs (AAI< 0,9) for the groups I, II and IV,
- Those who had an oedema of the lower limbs for the groups I, II and III,
- Those who were an alcohol-addict, a drug-addict or a tobacco-addict (over 10 cigarettes a day),
- Those whose full and entire co-operation throughout the study was doubtful.

4.2.4 Investigations: Clinical examination - Inclusion

In order to determine medical and surgical history, the physician performed a complete interrogation of the subject's background. The following examinations were also performed to check the general health of the subject:

- A 12-lead electrocardiogram,
- Measurements of the arterial pressure and the cardiac frequency,
- Echo Doppler of the lower limbs (arterial and venous),
- Measurement of the ratio of ankle-to-arm systolic pressures in both limbs.

After a physical examination, a 12-lead electrocardiogram, the measurements of the ratio of the ankle to brachial systolic pressure in both limbs, veins and arteries of abdominal and lower limbs examination by colour Duplex scanning. Each of these was performed in order to exclude the subjects with significant cardiovascular disease and classify them in one particular group defined above. The information for each participant was reported by the physician in an individual booklet presented in Appendix C. This booklet was confidential.

The main information for each subject was documented on a one-side page document. This document was also used to report technical information during the experimental protocol. For example, concerning the different calibration of devices, the temperature and hygrometry of the room, the possible problems during the measurements, the behaviour of the subject during the measurements, and any complementary information that could be useful for the interpretation of the results. The document used for this purpose is presented in Appendix D.

4.3 Materials and methods

4.3.1 Subjects

Twenty eight healthy Caucasian subjects participated in the present study. The participants included 17 young volunteers with a mean age of 24±0 years, weight of 65±2 kg, and height of 171±2 cm and 11 elderly volunteers with a mean age of 53±1 years, weight of 65±2 kg, and height of 162±2 cm. All volunteers gave their written informed consent to participate in the experimental protocol which was approved by our institutional review committee according to Helsinki Declaration. Since a homogeneous population is difficult to achieve when referring to arterial or venous disease, the experimental study has been performed for a healthy population of subjects only. No subject could be included either in group 3 or in group 4 with respect to the overall criteria of inclusion mentioned earlier. The study on non healthy participants will be conducted in the future.

4.3.2 Electrocardiogram (ECG)

The electrocardiogram (ECG) is a graphic recording of the changes occurring in the electrical potentials (in mV) between different sites on the skin (leads) as a result of cardiac activity.

The ECG thus reflects the electrical events connected with cardiac excitation and provides information about the anatomical orientation of the heart, the relative sizes of the heart chambers, heart rate, rhythm and origin of excitation, spread of the impulse, decay of excitation and disturbances in the above events, irrespective of whether they are due to anatomical, mechanical, metabolic or circulatory defects. The ECG gives no information on the concentration and pumping efficiency of the heart; these properties can only be judged on the basis of blood pressure, cardiac output, heart sounds in particular.

4.3.3 Ankle-to-arm systolic pressures

The ratio of ankle-to-arm systolic pressures is called the ankle to arm index (AAI). AAI at rest is widely used in the clinical diagnosis of peripheral arterial disease. From the literature in normal subjects, values for AAI range from 1.08±0.10 (mean±SD) to 1.18±0.08, Fronek *et al.* [28], Hirai *et al.* [38]. During lower extremity arterial disease, although AAI at rest decreases proportionally to the severity of arterial lesions, Carter [14], Carter [15], Ouriel *et al.* [75], Yao *et al.* [117], Yao [118], it can be normal in some patients suffering from mild to severe arterial stenosis. Thereafter the normal limit for AAI can hardly be defined. Nevertheless, AAI at rest has largely been used as a noninvasive predictor of cardiovascular risk and also as a sole test for the screening of lower extremity arterial disease in the general population. For these reasons, examination by colour Duplex scanning were performed in order to complete an accurate state of the arterial system of the participant.

4.3.4 Transcutaneous oxygen and carbon dioxide pressures

Transcutaneous oxygen pressure (tcpO2), based upon the electrochemical reduction of oxygen, was measured using a Clark-type oxygen sensing electrode, White *et al.* [113], Kram *et al.* [51]. Transcutaneous carbon dioxide pressure (tcpCO2) was measured using a Severinghaus-type carbon dioxide electrode. A combined transcutaneous oxygen pressure and carbon dioxide pressure electrode comprising a heating element, two temperature sensors, and the gas measurements electrodes in a single unit was used (TCM3 Radiometer - Copenhagen - Denmark) and placed distal to the splint. When the electrode was attached to the skin with a double-sided adhesive ring tape, the heat generated, automatically stabilised to 44.5°C, was transferred from the heat-

ing element via the silver body to the skin surface. This heating produced local vasodilation, increasing the permeability of the skin to oxygen and carbon dioxide, and allowing measurement on the skin surface. All tcpO2 and tcpCO2 measurements were made with the subjects breathing room air, and the data were expressed in millimetres of mercury and automatically corrected to 37°C.

4.3.5 Laser Doppler flowmeter

Cutaneous blood flow (LDF) of the foot was measured using a laser Doppler flowmeter (Periflux 4001, Perimed AB - Järfälla - Sweden) applied to the skin of the forefoot with a plastic holder. The helium-neon laser Doppler velocimeter uses a monochromatic light source at 780 nm. Conducted to the body surface via fibre optics, the laser light illuminates and permeates the skin in a diffuse way, Stern [103], Matsen *et al.* [58], Nilsson *et al.* [73], Engleheart *et al.* [21], Karanfilian *et al.* [48]. Back-scattered light is detected by sensitive photodetectors via a separate fibre in the probe. Doppler-shifted light, proportional to the product of velocity and the concentration of moving red blood cells within the surface capillaries of the skin, Nilsson *et al.* [73], is processed and expressed in arbitrary units (A.U). Comparison with non invasive techniques such as plethysmography or thermal clearance showed that LDF provides accurate measurement of skin blood flow in human limb, Johnson *et al.* [44] and Saumet *et al.* [85], and is used widely in the investigation of the skin microcirculation, Shepherd [93], Bongard *et al.* [11], Abu-Own *et al.* [2]. We have previously shown that cutaneous LDF is not influenced by underlying tissue blood flow, Saumet *et al.* [86].

4.3.6 Doppler scanning

Ultrasound imaging of the femoral vessels was performed with a 7 MHz linear electronic transducer (ACUSON 128XP10 - Mountain View - California - USA). Ultrasound coupling between skin and probe was achieved by a large amount of ultrasound transmission gel, avoiding direct contact influence of the probe with the skin. The femoral vessel was scanned in transversal plane and a regular segment of the common femoral vein was pointed with an indelible marker on the skin, very close to the saphenofemoral junction. The probe was then turned 90 degrees to display a longitudinal view of the vessel and to measure both arterial femoral velocity

(A.F.V.) and the venous femoral velocity (V.F.V.) distal to the saphenofemoral junction. Using a maximal true angle between the probe and the skin and an inclined Doppler axis of 20°, the complementary angle to align with the vessel axis was inferior to 60° in all cases. Both arterial and venous blood flow velocities were the average of the maximal velocities on a 8 seconds recording as previously reported by Janssen *et al.* [43], Abraham *et al.* [1], Abu-Own *et al.* [2] (included eventual arterial diastolic zero flow), and were not angle corrected.

4.3.7 Data acquisition system

The resulting analogue output laser Doppler signals, tcpO2 and tcpCO2 signals in both feet and the pressure in the full-leg splint were recorded by means of a data acquisition system (MP100, Biopac System Inc., Santa Barbara, California - USA) and further analysis was performed by a specific software (Acknowledge, Biopac System Inc., Santa Barbara, California - USA). The sampling acquisition rate was constant at 25 samples per second.

Lastly the heart rate and arm systolic and diastolic blood pressures were recorded throughout the experiment using an automatic 16 cm large cuff inflation system (Dinamap 1846SX/P, Critikon, Johnson & Johnson - Tampa, Fl. USA) in order to check the stability of the general haemodynamic parameters of the participant over the experiment.

4.3.8 Experimental protocol

A standard inflatable splint extending from the ankle to the upper thigh (Mast III-AT anti shock trousers, David Clark company, Worcester UK) was placed around the right leg. The skin of each subject was cleansed with the use of alcohol tabs at the selected measuring sites. The subject, fully equipped, was placed supine upon an examination table with a pillow under the head, in a quiet room for 20 minutes to allow stable conditions at rest. The room temperature was maintained at 25.4±0.2°C and the hygrometry was 58.7±0.8%. Once the measurements started, each subject was asked to lie immobile until the end of the experiment.

After measurements in the basal conditions were achieved, the splint was inflated to 10 mmHg and maintained for three minutes. During the last two minutes, the sonographic measurements were achieved by a well trained physician. Each step duration was 3 minutes in total. After this first step, the inflation of the splint was increased at 20 mmHg, then successively

increased by step of 20 mmHg. The first part of the experiment was ended when no decrease in LDF and tcpO2 was observed between two successive levels of splint pressure. The minimum values were deflned as the physiological zero of the participant, observed at the individual maximum reached splint pressure. During the second part of the experiment, the pressure of the splint was decreased by step of 20 mmHg until the total deflation of the splint was performed.

4.3.9 Initial statistical analysis

The statistical analysis which is presented below is often performed at the beginning of any experimental analysis. The task here has nothing in common with the modelling exercise which is discussed latter. The results are expressed as means ±SEM. Analyses of differences between paired values were carried out using the non parametric Wilcoxon matched-pairs signed-ranks test (applied within a single group) with the basal condition (splint not inflated) as the reference. The Mann-Whitney test, also called the rank sum test, is a non parametric test that compares two population means defined as the young participants and the elderly participants. The Mann-Whitney test was used to examine if there is any significant difference between the means. A p value of less than 0.05 was considered significant. The p value of a tested hypothesis is the probability of observing a value of the test statistic that is at least as inconsistent with the null hypothesis as the value of the test statistic actually observed. Therefore the smaller the p value, the stronger the evidence against the null hypothesis. The following symbols are used in the tables according to the p values, also referred to as the observed significance level, or the probability value:

* $p<0.05$

** $p<0.01$

*** $p<0.001$

Statistical computation was carried out with use of the Statistical Package for Social Sciences (SPSS Inc. Chicago, Ill.).

Pressure mmHg	LDF A.U	tcpO2 mmHg	tcpCO2 mmHg	A.F.V. $m.s^{-1}$	V.F.V. $m.s^{-1}$	n
0	11.6±1.8	71.1±3.6	39.4±1.4	0.22±0.02	0.15±0.02	17
10	8.6±1.3***	71.8±3.4	40.2±1.5*	0.17±0.01***	0.15±0.02	17
20	7.0±1.0***	71.1±3.7	40.5±1.5**	0.15±0.01***	0.12±0.02***	17
40	5.7±0.7***	69.6±3.8	41.2±1.6***	0.11±0.01***	0.08±0.01***	17
60	4.3±0.5***	62.0±4.4*	42.0±1.6***	0.07±0.01***	0.05±0.01***	17
80	3.6±0.5***	37.6±5.9***	45.0±1.8***	0.05±0.01***	0.04±0.01***	17
100	2.5±0.4*	23.6±7.6*	44.8±2.6*	0.04±0.01*	0.02±0.00*	6

Table 4.1: Table of measurements for young participants with increasing pressure in the splint

Pressure mmHg	LDF A.U	tcpO2 mmHg	tcpCO2 mmHg	A.F.V. $m.s^{-1}$	V.F.V. $m.s^{-1}$	n
Pmax-20	3.3±0.4***	7.9±2.6***	57.7±3.0***	0.10±0.01***	0.06±0.01***	17
Pmax-40	7.4±1.3**	30.7±5.9***	63.8±3.9***	0.14±0.01***	0.10±0.02**	17
Pmax-60	9.3±1.6	59.8±4.7**	50.7±2.9***	0.17±0.01***	0.13±0.02	17
Pmax-80	13.0±2.3	71.0±3.0	42.8±1.6***	0.21±0.01	0.19±0.02	17
Pmax-100	11.5±5.7	78.3±2.6	39.8±1.6	0.23±0.01	0.17±0.02	6

Table 4.2: Table of measurements for young participants with decreasing pressure in the splint

4.4 Results for the young participants

All subjects had stable heart rate and arm systolic and diastolic blood pressures over the full duration of the experiment (n=17). These measured parameters did not change significantly: from 107±2 mmHg, 61±1 mmHg, 62±2 min^{-1} to 113±3 mmHg, 64±2 mmHg, 64±3 min^{-1} over the first three minutes and the last three minutes of the experiment respectively. The results of various splint pressures on laser Doppler flow, tcpO2, tcpCO2, venous and arterial femoral velocities are summarised in the table 4.1 for the inflated pressures and in the table 4.2 for the deflated pressures for all subjects. The minimum values were reached at 80 mmHg in 11 subjects. Therefore only 6 subjects were observed at a pressure of 100 mmHg. The maximum pressure of the splint was defined as Pmax, and was used as the reference to analyse the decompressive part of the experiment. The mean pressure in the splint to reach the physiological zero was 87±2 mmHg for the overall of the participants. The p values were calculated considering the number of participants at each pressure.

A significant decrease in LDF (25.9 % compared to the mean resting value) measured on the forefoot yet occurred when the external pressure was 10 mmHg ($p<0.001$). The LDF continued

to decrease until a minimum skin blood flow level of 2.5±0.4 A.U (78.4 % decrease compared to the basal condition). In the second part of the experiment, LDF increased progressively from 3.3±0.4 A.U at Pmax-20 mmHg to 14.7±2.7 A.U when the splint was totally deflated: this maximum value was reached at different splint pressures (Pmax-80 mmHg for 11 participants, and Pmax-100 mmHg for the other 6 participants).

Although it trended to decrease, no significant change was found for tcpO2 before the splint pressure reached 60 mmHg. However tcpCO2 values increased significantly ($p<0.05$) at 10 mmHg and further increased up to a value of 63.8±3.9 mmHg at Pmax-40 mmHg corresponding to an increase of 61.9 % compared to the mean resting value. When the splint pressure was released, tcpO2 increased up to a value of 78.3±2.6 mmHg, and the tcpCO2 decreased to 39.8±1.6 mmHg.

The skin microcirculation in the left leg, used as the control leg, showed no significant change over the whole experiment: LDF, tcpO2 and tcpCO2 were stable from the resting period (6.8±0.9 A.U, 83.9±1.9 mmHg and 43.8±4.2 mmHg) to the end of the experiment (7.3±0.9 A.U, 82.6±2.0 mmHg and 43.0±3.6 mmHg).

There was no observed beneficial effect at a splint pressure of 10 mmHg. A 20 mmHg compression reduced significantly ($p<0.001$) the V.F.V.: an average of 20.0% decrease compared to basal condition. The V.F.V. further decreased as the applied pressure was increased. At a splint pressure of 100 mmHg, the maximal decrease in venous velocity compared to resting value was 86.7 % ($p<0.05$). As the pressure in the splint was decreased, the V.F.V. increased progressively to a value of 0.20±0.02 $m.s^{-1}$, although this value corresponded to Pmax-80 mmHg for 11 participants, and Pmax-100 mmHg for the other 6 participants).

The A.F.V. decreased for external pressure as low as 10 mmHg ($p< 0.001$). The minimum A.F.V. was 0.04±0.01 $m.s^{-1}$ at 100 mmHg, representing a 81.8 % decrease compared to the basal velocity ($p<0.05$). In the second part of the experiment, the A.F.V. increased up to a value of 0.22±0.01 $m.s^{-1}$at the total deflation of the splint which was different according to each participant.

The relationship between externally applied splint pressure and the different observed parameters are all summarised in Figure 4-1.

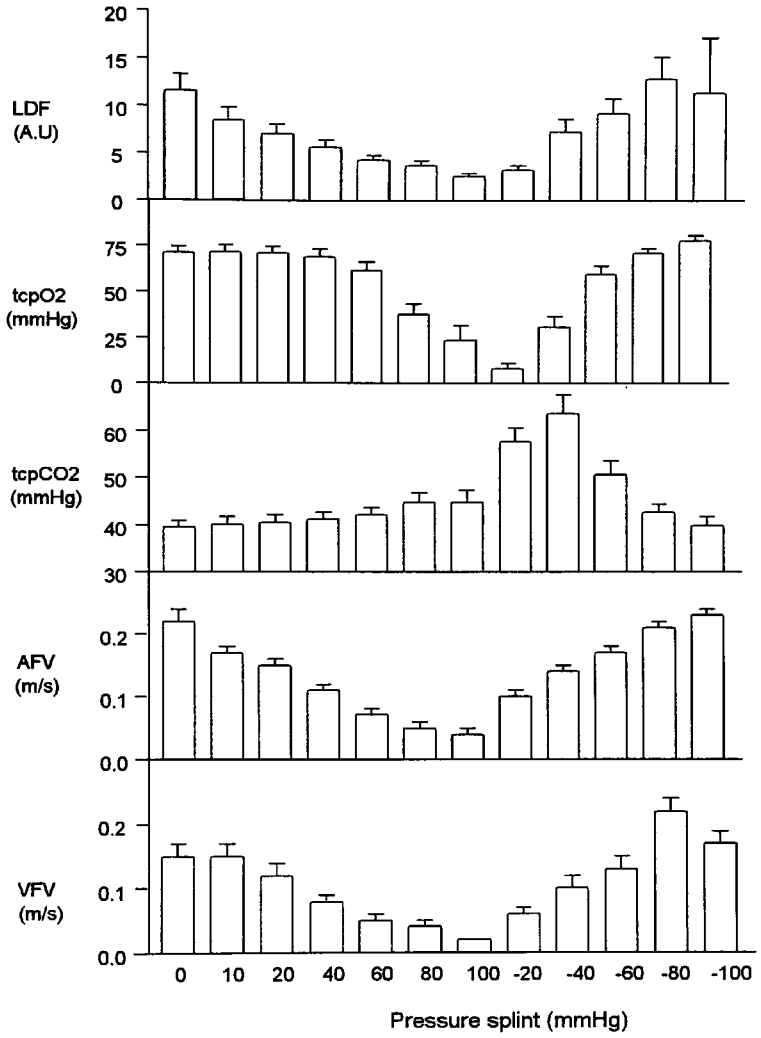


Figure 4-1: Young participants (n=17)

Pressure mmHg	LDF A.U	tcpO2 mmHg	tcpCO2 mmHg	A.F.V. $m.s^{-1}$	V.F.V. $m.s^{-1}$	n
0	13.7±3.0	62.5±3.7	40.7±1.1	0.16±0.01	0.11±0.01	11
10	9.4±2.3*	63.0±3.1	40.9±1.0	0.14±0.02*	0.10±0.02	11
20	8.0±1.7*	63.6±2.5	41.0±1.1	0.10±0.01**	0.08±0.02	11
40	5.3±0.5*	62.8±2.3	41.7±1.0*	0.08±0.01**	0.08±0.02	11
60	5.0±0.8*	60.6±2.8	42.4±1.1**	0.06±0.01**	0.05±0.01**	11
80	4.3±0.6**	50.8±4.9**	42.9±1.2**	0.06±0.01**	0.05±0.01**	11
100	3.4±0.5**	31.7±5.3**	45.3±1.5**	0.04±0.01**	0.03±0.01**	11
120	2.8±0.7	15.6±5.9	45.7±2.7	0.05±0.01	0.03±0.03	3

Table 4.3: Table of measurements for elderly participants with increasing pressure in the splint

Pressure mmHg	LDF A.U	tcpO2 mmHg	tcpCO2 mmHg	A.F.V. $m.s^{-1}$	V.F.V. $m.s^{-1}$	n
Pmax-20	3.4±0.4**	7.5±1.9**	55.6±2.2**	0.08±0.01**	0.05±0.01*	11
Pmax-40	6.3±0.8*	23.6±3.8**	61.0±3.5**	0.12±0.02*	0.07±0.01*	11
Pmax-60	11.2±3.4	47.7±4.8**	52.6±4.6**	0.15±0.01	0.09±0.01	11
Pmax-80	10.4±2.0	57.5±3.0*	45.3±2.0**	0.16±0.01	0.11±0.02	11
Pmax-100	16.9±4.5	61.6±3.7	42.7±1.3**	0.20±0.03	0.12±0.01	11
Pmax-120	14.7±8.3	66.9±5.9	42.1±2.7	0.20±0.07	0.13±0.03	3

Table 4.4: Table of measurements for elderly participants with decreasing pressure in the splint

4.5 Results for the elderly participants

All subjects had stable heart rate and arm systolic and diastolic blood pressures over the full duration of the experiment (n=11). These measured parameters did not change significantly: from 121±4 mmHg, 73±2 mmHg, 63±2 min^{-1} to 117±4 mmHg, 73±3 mmHg, 64±2 min^{-1} over the first three minutes and the last three minutes of the experiment respectively. The results of various splint pressures on laser Doppler flow, tcpO2, tcpCO2, venous and arterial femoral velocities are summarised in the table 4.3 for the inflated pressures and in the table 4.4 for the deflated pressures for all subjects. The minimum values were reached at 100 mmHg in 8 subjects. Therefore only 3 subjects were observed at a pressure of 120 mmHg. The mean pressure in the splint to reach the physiological zero was 105±3 mmHg for the overall of the elderly population.

A significant decrease in LDF (31.4 % compared to the mean resting value) measured on the forefoot already occurred when the external pressure was 10 mmHg ($p<0.05$). The LDF continued to decrease until a minimum skin blood flow level of 2.8±0.7 A.U at 120 mmHg

(79.6 % decrease compared to the basal condition). In the second part of the experiment, LDF increased progressively to reach a value of 18.9±4.5 A.U when the splint was totally deflated, although this occurred at Pmax-100 mmHg for 8 participants and at Pmax-120 mmHg for the other 3 participants.

No significant change was found for tcpO2 until the splint pressure reached 80 mmHg. However tcpCO2 values increased significantly ($p<0.05$) at 40 mmHg and further increased up to a value of 61.0±3.5 mmHg at Pmax-40 mmHg. When the splint pressure was released, tcpO2 increased to a value of 62.7±2.7 mmHg, and the tcpCO2 decreased to 42.2±1.2 mmHg according to individual deflation splint pressures.

The skin microcirculation in the left leg, used as the control leg, did not show any significant changes over the whole experiment: LDF, tcpO2 and tcpCO2 were stable from the resting period (7.9±1.8 A.U, 69.7±3.3 mmHg and 37.8±0.9 mmHg) to the end of the experiment (8.2±1.6 A.U, 67.4±2.8 mmHg and 38.9±0.7 mmHg).

There were no observed beneficial effect at a splint pressure of 10 mmHg. A 60 mmHg compression reduced significantly ($p<0.01$) the V.F.V.: an average of 54.5 % decrease compared to basal condition. The V.F.V. further decreased to 0.03±0.03 $m.s^{-1}$ as the applied pressure was increased. At a splint pressure of 120 mmHg, the maximum decrease in venous velocity compared to resting value was 72.7 %. As the pressure in the splint was decreased, the V.F.V. increased progressively to a value of 0.13±0.01 $m.s^{-1}$, although this value corresponded to Pmax-100 mmHg for 8 participants, and Pmax-120 mmHg for the other 3 participants.

The A.F.V. decreased for external pressure as low as 10 mmHg ($p< 0.05$). The minimum A.F.V. was 0.04±0.01 $m.s^{-1}$ at 100 mmHg, representing a 75.0 % decrease compared to the basal velocity ($p<0.01$). In the second part of the experiment, the A.F.V. increased up to a value of 0.21±0.03 $m.s^{-1}$at the total deflation of the splint which was different according to each participant.

The effect of externally applied splint pressure on the different observed parameters are reported in Figure 4-2.

Significant differences between young and elderly participants in the average of both general characteristics and measured parameters were observed. The test was carried out by the Mann-Whitney test. The results of the test are reported in Table 4.5. The test was performed on

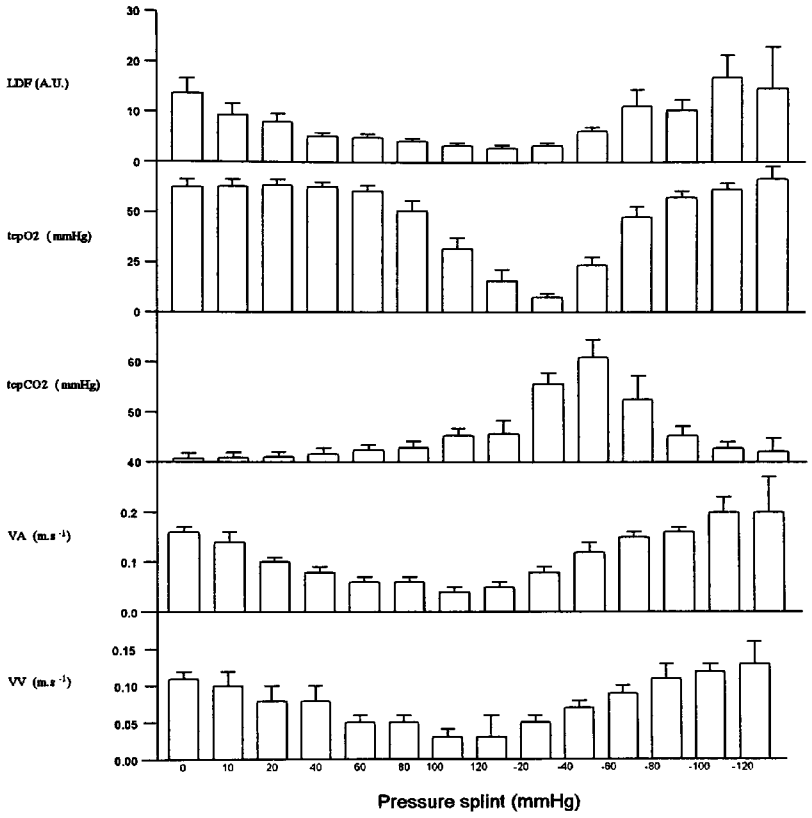


Figure 4-2: Elderly participants (n=11)

Variables	Young values	Elderly values	2-tailed p
age	24	53	0.0000
IPSC	1.08	1.15	0.0021
Pmax	87	105	0.0003
Height	171.4	162.0	0.0026
tcpO2 at 10 mmHg	71.8	63.0	0.0225
tcpO2 at 20 mmHg	71.1	63.6	0.0154
tcpO2 at 40 mmHg	69.6	62.8	0.0363
tcpO2 at Pmax-60 mmHg	59.8	47.7	0.0363
tcpO2 at Pmax-80 mmHg	71.0	57.5	0.0033
tcpO2 at Pmax-100 mmHg	78.3	61.6	0.0036
A.F.V. at rest	0.22	0.16	0.0127
A.F.V. at 20 mmHg	0.15	0.10	0.0303
A.F.V. at 40 mmHg	0.11	0.08	0.0355
A.F.V. at Pmax-80 mmHg	0.21	0.16	0.0249
V.F.V. at Pmax-80 mmHg	0.19	0.11	0.0089

Table 4.5: Table of results showing the Mann-Whitney significant differences between young and elderly participants

common variables between both groups. However it is obvious that at 120 mmHg and Pmax-120 mmHg the test was not possible, as this pressure was reached in few cases in the elderly group only. When the difference was significant between the groups I and II on the recorded signals, the values for the elderly participants were always less than the corresponding values for the young participants.

4.6 Discussion

The findings of the present investigation demonstrated a significant impairment of A.F.V. and LDF (for participants from both groups), and tcpCO2 (for participants from group I only) with compressive value as low as 10 mmHg, although V.F.V. and tcpO2 were not decreased. On the other hand, for our experimental conditions, tcpO2 appears less relevant than both LDF and tcpCO2 to evaluate local micro-circulatory impairment.

Very little information is available regarding the effect of external compression on venous blood flow in the total extremities, Ashton [5], Ashton [6]. On the other hand, few results are available for the effect of uniform compression on arterial blood flow, Halperin *et al.* [33], since most recent studies have been performed on the effects of local applied pressure on the

microcirculation by Mayrovitz *et al.* [60], [61]. Even less is known regarding the effects of externally applied pressure on both venous and arterial blood flow, and distal microcirculation.

The applied pressure produced by elastic compression or bandages can be classified according to the degree of compression, Blair *et al.* [9]. The compression bandages range from 14 to 17 mmHg for the light compression bandages, from 18 to 24 mmHg for moderate compression bandages, from 25 to 35 mmHg for high compression bandages, and is up to 60 mmHg for extra high-performance compression bandages, Thomas [107]. Nevertheless as already emphasised, the pressure values used in patient management is in the same range as those which could lead to an arterial ischaemia.

Sabri *et al.* [83] found that a 5 mmHg inflatable splint compression produces a non-significant increase in the femoral arterial and venous flows. Unfortunately, the arterial flow was measured in dogs, whereas the venous flow was measured in humans. They mentioned that a higher compression pressure is required before any significant decrease of the femoral venous blood flow can be seen. Inversely, Spiro *et al.* [101] mentioned an increase of 13% of the femoral vein flow in both limbs at 5 mmHg by inflatable splint, but no statistical analysis was made in this study. However they concluded that the optimum pressure usually lies between 5 and 12 mmHg but may well vary from patient to patient depending on such factors as limb adiposity, limb circumference, the presence of lymphoedema, or previous episodes of thrombosis. Our results are consistent with the Sabri *et al.* investigation, as we showed that there was no significant increase of the femoral venous velocity at a 10 mmHg compression and that the venous velocity decreased significantly at 20 mmHg splint pressure.

Otherwise we found that a significant decrease of 19.0 % compared to resting value in maximal arterial inflow occurred for splint pressure as low as 10 mmHg. In agreement with our investigation, Sabri, *et al.* [83] showed that " a compression pressure exceeding 5 mmHg produces a progressive diminution of the femoral arterial blood flow ". Halperin *et al.* [33] reported also that an external applied pressure of 10 mmHg was sufficient to reduce the arterial circulation in normal limbs. They attributed the resultant decrease of arterial inflow and venous outflow to two possible factors: first, a reduction of arteriovenous pressure gradients, and, secondly, a decrease in the calibre of small vessels in the compressed area that caused an increase in resistance to flow. Consistently with arterial flow decrease produced by 10 mmHg,

the skin blood flow showed a significant decrease at 10 mmHg.

The tcpO2 decrease with increasing pressure shown in recumbent subjects found in the present study is in agreement with Gaylarde *et al.* [32] who mentioned that a compression of the lower limb whilst the subject is recumbent leads to a fall in tcpO2. This author suggested that when the patient is confined to bed, only lightweight stockings (the applied pressure lies between 5 and 10 mmHg) are safe in the prophylaxis of post-operative deep-vein thrombosis. However our results suggest that tcpO2 alone does not interpret the arterial haemodynamics properly in our experimental conditions. Indeed a significant decrease was observed only at 60 mmHg with tcpO2 readings. Maybe the skin blood flow impairment due to a splint pressure up to 60 mmHg was not sufficiently important. On the other hand; for normal arteriolar pressure values, tcpO2 mainly reflects arterial pO2. TcpO2 becomes flow dependant only when arterial pressure is reduced below a certain threshold, Colin *et al.* [18]. The late decrease of the tcpO2 values found in the present work may result from relative uncompromised distal arteriolar pressures. Since arteriolar pressure in the foot was not recorded in the present study, this hypothesis cannot be validated. Nevertheless for a pressure as low as 10 mmHg, tcpCO2 increased significantly, while LDF decreased significantly. We hypothesise that pH increased and that a distal microcirculation impairment was already observed on the forefoot. Andreozzi *et al.* [3] already showed that a dissociation between tcpO2 and tcpCO2 exists. In a further study, Andreozzi *et al.* [4] mentioned that "in some cases, the tcpO2 cannot provide correct assessment of the risk of skin necrosis, while tcpCO2 measurement could". On the other hand, Caspary *et al.* [16] have mentioned that a significant difference exists between tcpO2 and LDF changes at the forefoot due to different physiological stresses. Therefore, tcpO2 measurement on its own may not be a sufficient tool in our experimental conditions to control the distal microcirculation.

From this study it can be seen that positive pressure on the full leg provided no significant beneficial effect on femoral venous blood velocity. Whereas we showed that for an external uniform pressure as low as 10 mmHg, significant impairments in both arterial inflow of the lower limb and microcirculation of the forefoot appeared in recumbent healthy young subjects. Although such a result was found in healthy volunteers, the technique used in the present work is an interesting approach in the understanding of the compression effects. A study of

patients with vascular disease, both arterial and venous, would be relevant. It might allow a better understanding of potential beneficial and harmful effects of compression in such patients groups. Further work and additional data will be necessary to sort out these issues.

Chapter 5

STATISTICAL MODELLING APPROACH AND RESULTS

5.1 Introduction

The objective of this chapter is to develop a mathematical model using the data collected from the experiment presented in the previous chapter. The statistical analyses that have been conducted to produce this model are reported in the present chapter.

As mentioned in Chapter 4, the recorded signals were the pressure in the splint, the laser Doppler flow, the transcutaneous oxygen and the transcutaneous carbon dioxide pressures. For convenience, they were mathematically denoted by $p(t), l(t), o(t), c(t)$ respectively. The arterial and venous velocities were denoted by $va(t)$ and $vv(t)$ respectively. For ease of notation the following was also used $o(t)$ as o, $o(t)^2$ as $o2$, $o(t-1)$ as o_1, $o(t-2)^4$ as o_24, and so on. These initial recorded data vectors have been identified as being significant by the clinicians to evaluate the vascular effects of an external compression. It is therefore the aim of this chapter to investigate the strength and the type of the links between these justified variables in detail. It is then possible to produce a model which will describe the underlying structural relationships that exists between the variables.

The experimental results consisted of data which were of different types. The general characteristics of the person (age, sex, height, weight) represented one value for each subject. The recorded variables (p, o, c, l) were sampled at 25 observations per second, which represented

for the complete experiment for each participant approximately $25 * 60 * 3 * 12 = 54000$ observations for those who had 100 mmHg as a maximum pressure splint. These recorded data represented more than 30 MB for all subjects. The measured variables $va(t)$ and $vv(t)$ were recorded once at every step of pressure throughout the experiment, which represented from 10 to 14 observations for each person. Hence a huge volume of data was generated which consisted of several types, and that were incompatible in a single micro or macro modelling approach. It was obvious that preliminary data classification was needed before further detailed analyses could continue. Many ways were possible to classify them into different groups based on the data description.

The main progressive steps of the procedure for statistical analysis modelling of the experimental results are summarised in a flow chart given in Figures 5-1 and 5-2. The data were collected during the experiments for 28 subjects. As discussed above, it was necessary to classify the data into groups. The first relevant classification separated the measured variables from the general characteristics of the subject. A further sub-grouping was then possible within the six measured variables according to their random variability. At this stage the three variables p, o, c were retained in the process, whereas va and vv were delayed to be included later in the analysis. The variable (l) was removed completely for its non consistency between subjects. Finally, it was noted that the o and c variables were complementary, and so only two variables (o and p) remained. As a result of the huge amount of data, the next step was to determine the optimum sampling interval to extract the best information from the data. This will be discussed in section 5.3. It was then possible to start the modelling process. This was realised in different stages, where each represented an improvement on the previous stage. All these stages are detailed in section 5.4. At the end of this section, an expression for o as a power function of past history in terms of p and o was obtained. Two options were available to continue the modelling either in a non steady state condition or in a steady state condition. Both strategies have been tried and they are developed in section 5.5. Only the steady state model appeared to be of significant benefit and the other option was not pursued. The identification of the model in a steady condition was achieved. This was achieved in several steps which resulted in a common pattern for all subjects. Full details of the model specification is presented in this section. Finally the model characterisation, presented in section 5.6, was possible (taking into

account the variables, in a discrete form, which were delayed from the start of the modelling process). A general discussion on the final model will complete this chapter.

5.2 Data selection

Data collected in the experimental investigation varied in nature. As mentioned earlier the data obtained from the experimental database were:

- either single valued for each person (age, sex, weight, height),
- or single valued for each step of pressure for all subjects (va and vv),
- or were recorded at 25 sample per second for the entire population (p, o, c, l).

As explained above, the resulting database was complicated. It was then essential to organise them to make the analysis easier. Indeed grouping is one of the most common methods for organising data. In this section, the classification of variables which were characteristically different is discussed, and the various stages of grouping were justified.

5.2.1 Initial classification

The aim of the initial stage was to group the available data based on some clearly identified characteristics.

The characteristics of the subject have been noted in the physical examination preceding the inclusion of the subject in the experimental protocol. These include age, sex, height and weight of the subject. These variables were time-independent.

The six measured variables (p, o, c, l, va and vv) were extracted from the database built during the experiment itself. These variables were time-dependent.

This difference between time-independence and time-dependence was the basis for future analysis. The modelling strategy was to develop a common pattern using all time-dependent variables, which will accomodate the time-independent variables at a later modelling stage.

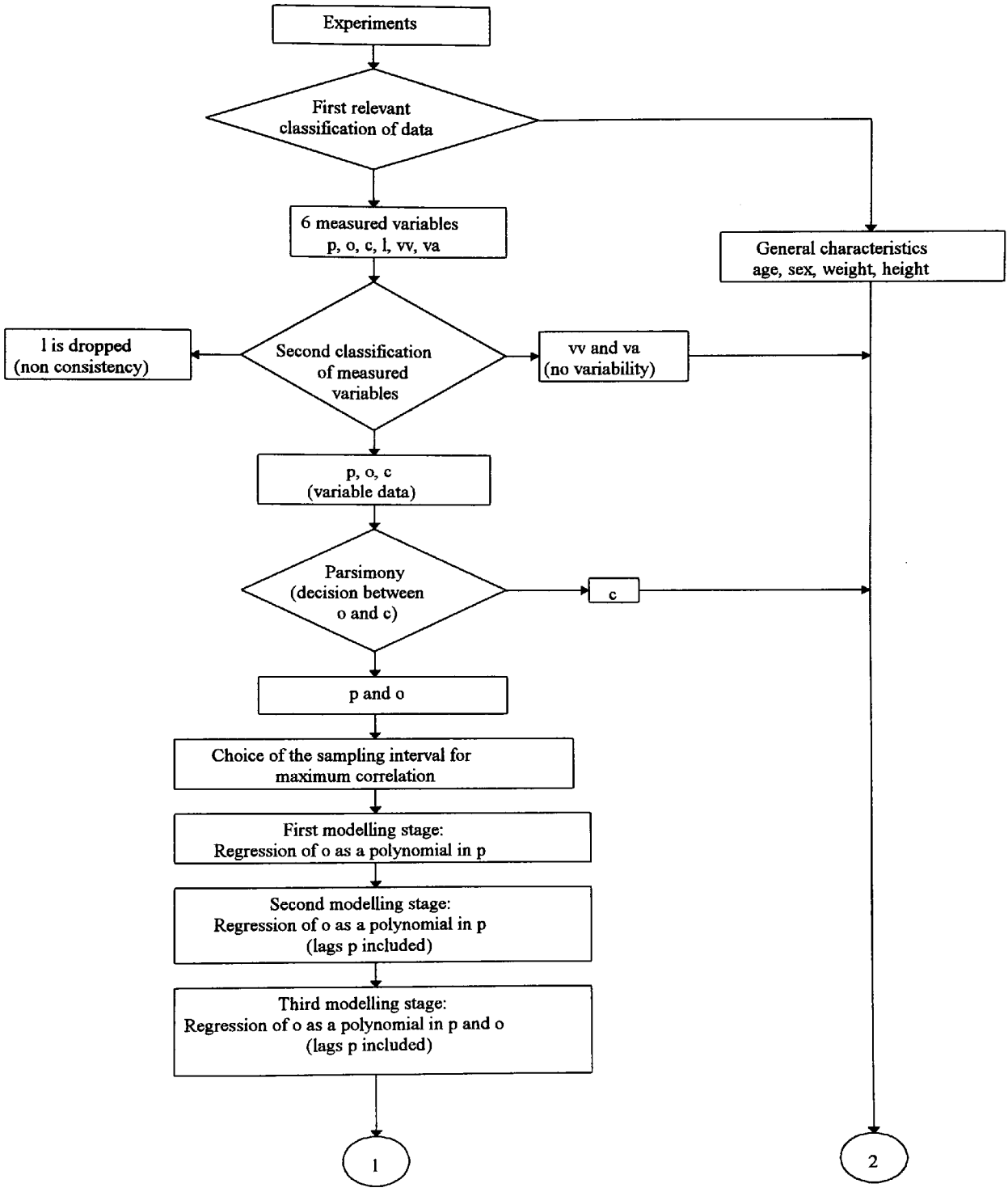


Figure 5-1: Flow chart (first part)

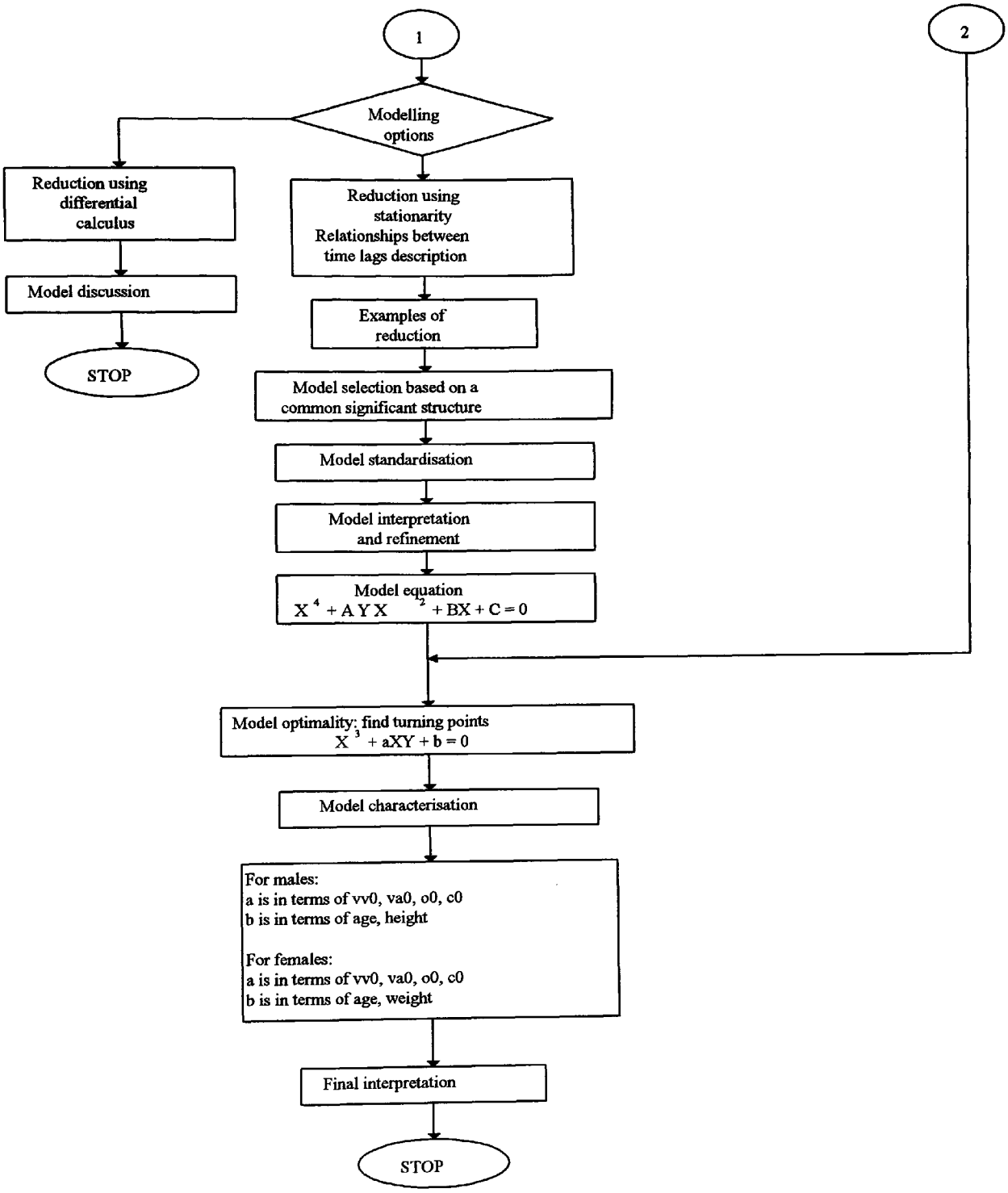


Figure 5-2: Flow chart (second part)

5.2.2 Classification of time-dependent variables

A more detailed observation regarding the remaining six time-dependent variables indicated that it was possible to make further sub-groupings. This was true as a degree of incompatibility could be observed within the time-dependent variables.

Each of the vectors (p, o, c, l) have been recorded at 25 observations per second and showed high variability, whereas va and vv were single valued for each step of changing pressure. Therefore va and vv might be considered in the same logical way as the general characteristics data and be included at a later stage in the modelling procedure. To be compatible with the general characteristics, va and vv will have to be considered as single values.

With respect to p, o, c and l, a further classification was made. A detailed investigation recorded of l values for different subjects did not show any pattern of consistency. In particular, some subjects showed a significant decrease of l corresponding to the increase in the splint pressure, whereas some others did not show any significant changes during the whole experiment. As l represented the signal recorded by the laser Doppler flowmeter, which was highly sensitive to the external environment, some of these inconsistencies were expected. Hence it did not reflect considerably patient's underlying characteristics, l was not considered further.

Therefore three variables remained in the process: p, o and c, which presented high visible random variability.

5.2.3 Parsimony

In modelling, one of the common strategies is to avoid over-parameterisation. To construct models, the minimum number of independent variables must be involved from which maximum information can be extracted. This is generally known as parsimony.

In this case, the level of transcutaneous oxygen and carbon dioxide, o and c, were clearly physically related as it was shown in Figures 4-1 and 4-2 in Chapter 4. These two variables were complementary in the sense that they were experimentally related for all subjects. The level of c usually started to increase when o reached a low level. The choice between o and c at this stage was arbitrary. It was decided to consider c in a later stage in the modelling process. To be compatible with the remaining variables which will be included later (general characteristics, va and vv), c will have to be presented as a single value.

Following this reduction only p and o remained in the analysis at this stage.

5.3 Choice of the sampling interval for maximum correlation

The initial sampling rate (25 samples per second) was imposed by the clinical instruments used for the experiments. In these conditions, the created database was too large and led to different types of problems such as computer storage, time consumption and data were very long and difficult to analyse.

It was therefore logical to consider ways of reducing the sample size. Such a reduction had to be made in a way that the integrity of the information provided by the data is preserved. The reduction had also to maximise the information content. A direct method to implement this achievement was to consider the way in which the variables p and o were correlated with respect to variable sampling intervals. For this purpose, different experiments with different sampling intervals were conducted. The sampling interval varied between 1 and 25 samples per second.

The choice of the sampling interval was crucial on its practical implication for future research because it was important that the sample be representative. In other words, the sample should reflect as closely as possible the relevant characteristics of the population under consideration. The implications were thus on the validity and significance of future research as well as its economic importance. Therefore the goal in sampling was to find the optimal sampling interval to extract the best information from the entire data.

To determine the effect of the sampling rate, the position or the size of the window over the full recorded database, the correlation between p and o was measured. The results are presented in Table 5.1.

To highlight the effects of the sampling rate, a graph is presented in Figure 5-3 for the correlation between p and o during the first drop of o over steps of 80 to 100 mmHg.

The results indicate that choosing a sampling interval in excess of 8 samples per second is counter productive. However a great consistency can be observed for a common optimality region between 2 and 7 samples per second. The existence of the optimum region suggests that there is an optimum sampling rate which maximises the information content of the experiment.

Sampling rate	Before the first drop of o(t) over steps of 20 to 60 mmHg	During the first drop of o(t) over steps of 80 to 100 mmHg	After the first drop of o(t) over steps of Pmax-80 to Pmax-100 mmHg	Entire data
25	-0.5358	-0.8583	-0.7399	-0.7411
24	-0.5493	-0.8587	-0.7652	-0.7411
23	-0.5561	-0.8589	-0.7773	-0.7411
22	-0.5599	-0.8591	-0.7849	-0.7411
21	-0.5631	-0.8593	-0.7906	-0.7411
20	-0.5656	-0.8595	-0.7950	-0.7411
19	-0.5677	-0.8597	-0.7984	-0.7412
18	-0.5694	-0.8600	-0.8013	-0.7413
17	-0.5706	-0.8602	-0.8039	-0.7412
16	-0.5717	-0.8605	-0.8060	-0.7413
15	-0.5728	-0.8606	-0.8080	-0.7414
14	-0.5737	-0.8608	-0.8093	-0.7414
13	-0.5745	-0.8609	-0.8106	-0.7415
12	-0.5755	-0.8610	-0.8116	-0.7415
11	-0.5762	-0.8611	-0.8124	-0.7416
10	-0.5770	-0.8612	-0.8134	-0.7415
9	-0.5776	-0.8613	-0.8143	-0.7418
8	-0.5783	-0.8613	-0.8151	-0.7417
7	-0.5789	**-0.8614**	-0.8156	-0.7418
6	-0.5798	**-0.8614**	-0.8161	-0.7418
5	-0.5805	**-0.8614**	**-0.8168**	-0.7420
4	-0.5814	**-0.8614**	-0.8164	-0.7418
3	-0.5819	-0.8612	-0.8144	**-0.7421**
2	**-0.5826**	-0.8610	-0.8095	-0.7420
1	-0.5791	-0.8604	-0.7840	-0.7418

Table 5.1: Correlation results between p and o for variable sampling intervals

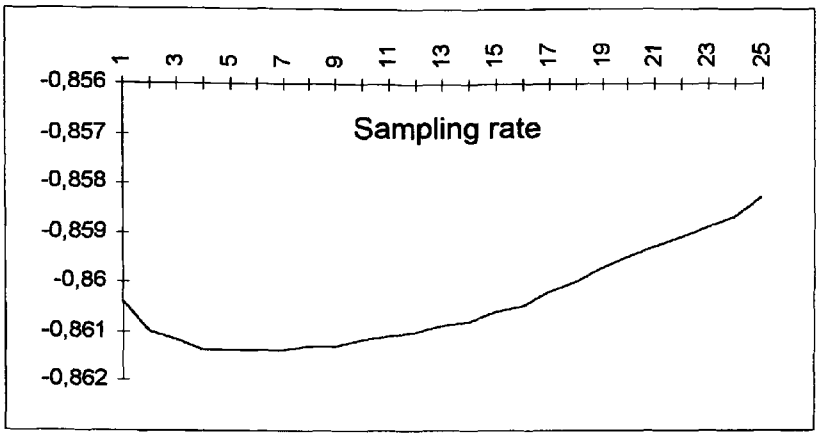


Figure 5-3: Correlated values between p and o for variable sampling intervals during the first drop of o over steps of 80 mmHg to 100 mmHg.

There are several implications of this analysis:

1. Economic significance:

   - Management of large data set: the large increase in the sampling rate did not improve the correlation between p and o. In fact, it reduced it.
   - Large increase in the sampling rate caused a problem in data management and storage.
   - Instruments for similar purpose could be design with a smaller sampling rate in view, which may cost less.

2. Past research: in previous experiments, no particular attention has been paid to sampling rates to the best of the author's knowledge.

3. Future research: our results indicate that the maximum information content can be achieved by a relatively small sampling rate.

In order to minimise the sample size without loss of significant information, a sampling rate of 1 was found to be appropriate for the analysis. Therefore the data was resampled at one sample per second. This rate was chosen to give a good balance between the accuracy of the database and the size of the file related to the computer limitations.

```
Variable(s) Entered on Step Number  3..    P4

Multiple R            ,57429          Analysis of Variance
R Square              ,32980                              DF       Sum of Squares      Mean Square
Adjusted R Square     ,32889          Regression           3        238422,12721       79474,04240
Standard Error      14,80310          Residual          2211        484500,14646         219,13168

                                      F =      362,67710       Signif F =  ,0000

---------- Variables in the Equation ----------

Variable             B         SE B        Beta         T  Sig T

P                ,554862     ,065550   1,015742     8,465  ,0000
P2              -,011779     ,001134  -2,162905   -10,386  ,0000
P4          3,69091E-07  5,8391E-08     ,668195     6,321  ,0000
(Constant)     80,335275     ,756283                106,224  ,0000

End Block Number   1   POUT =     ,100 Limits reached.
```

Figure 5-4: Linear regression results for the participant CHE027 obtained using SPSS

5.4 Model development

5.4.1 First modelling stage

At an initial stage, a preliminary relationship between p and o is desirable. In the first instance, it was natural to express this relationship by means of a polynomial to determine the dominant coefficients. Therefore o was expressed as a polynomial in p. Regression analysis was the statistical procedure that has been used to develop the polynomial. In the analysis, o was the dependent variable, and p was the independent variable. Other functional forms for o in terms of p could have been developed but it was noted that they would have a polynomial approximation.

An attempt was made to express o in terms of p to an unspecified degree. The results of the analysis are presented in Figure 5-4. To emphasise them, Figure 5-5 shows both predicted values from the multiple linear regression analysis and also the original signal o.

The regression analysis revealed no significant relationships. The highest R square that could be obtained was 0.33 with only powers of p up to and including 4. The weakness of the results demonstrated a failure of this first trial.

A possible reason for the failure of this polynomial was thought to be due to the nature of the recorded p values. Indeed p values present steps of 10 or 20 mmHg. These values

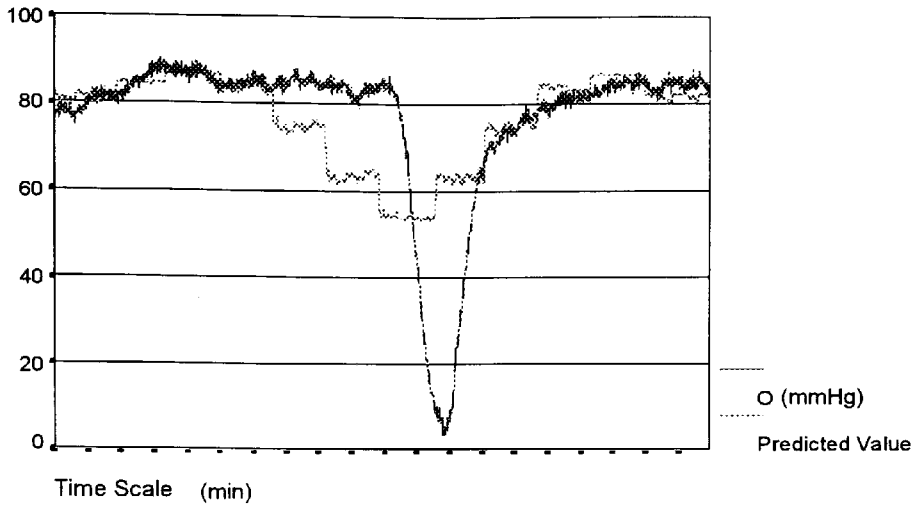


Figure 5-5: Predicted variable for $o(t)$ and original $o(t)$ for the participant CHE027

were recorded during the experiment according to the shape presented in Figure 5-6 with high variability within the steps.

This can obviously create modelling problem. Thus a new variable has been introduced in the modelling process to remove the steps in p. A causal transformation was used to create this new variable representing the variability of p. This variable was denoted by p' and was defined as follows:

$$p' = \frac{p - p_m}{p_m} * 100$$

with p_m the mean pressure at every step of pressure.

The regression analysis between p' and o did not improve the results. The failure of these regressions imply that a more general functional relationship between p and o needed to be considered.

Figure 5-6: Recorded values of p (in mmHg) showing the variability

5.4.2 Second modelling stage

To develop this relationship, it was necessary to re-examine the physical process. As a natural phenomena, it is clear that there will be a time delay between the application of instantaneous impulse pressure and the resulting oxygen level response. Such properties may be represented by time lag function in the modelling process, Priestley [79]. A polynomial which includes lagged terms of the following form will then be considered:

$$o_{predicted}(t) = a * p(t) + b * p(t)^2 + c * p(t)^3 + d * p(t)^4 + e * p(t-1) + f * p(t-1)^2 + ...$$

These representations are common, there are some notable examples in the literature: Young [119], Young *et al.* [120], Tong [108]. The estimates of the parameters of the above regression equation together with their significance levels are presented in Figure 5-7.

```
Variable(s) Entered on Step Number  3..    P_23

Multiple R           ,79879          Analysis of Variance
R Square             ,63807                          DF       Sum of Squares      Mean Square
Adjusted R Square    ,63760          Regression           3       901909,24886     300636,41629
Standard Error     14,90761          Residual          2302       511588,91088        222,23671

                                     F =    1352,77567       Signif F =  ,0000

------------------ Variables in the Equation ------------------

Variable              B         SE B       Beta          T  Sig T

P_22            ,005292      ,001854     ,692701     2,854  ,0044
P_23       -2,99782E-04  4,2999E-05  -3,866146    -6,972  ,0000
P_24        1,89119E-06  2,5108E-07   2,444872     7,532  ,0000
(Constant)    65,448036      ,577654              113,300  ,0000

End Block Number   1   POUT =     ,100 Limits reached.
```

Figure 5-7: Linear regression results for the participant GUI032 obtained using SPSS

The regression analysis displayed only the most significant components. The analysis of this particular case indicated the significance of the three variables ($p(t-2)^2$, $p(t-2)^3$, $p(t-2)^4$). This produced a major improvement with respect to the R square as compared to the previous section.

The predicted oxygen level is presented with the original data in Figure 5-8. This graph demonstrated that this regression is not yet satisfactory. Further analysis of the process is needed.

5.4.3 Third modelling stage

In the previous section, it was demonstrated that an expression purely in p with delayed terms was not sufficient to express the changes in o. Therefore it was once again necessary to re-examine the physical process. The detailed examination of the physical process, it was noticed that a large difference between oxygen level in resting conditions for all subjects existed. Therefore it was natural to assume that the oxygen level at a particular time t was produced as result of a level at previous time and changes caused through the application of the splint pressure. This suggested that the model will be based on a nonlinear ARMA (Auto Regressive Moving Average) model, Box and Jenkins [12] and Priestley [79].

A new model was represented in the following form:

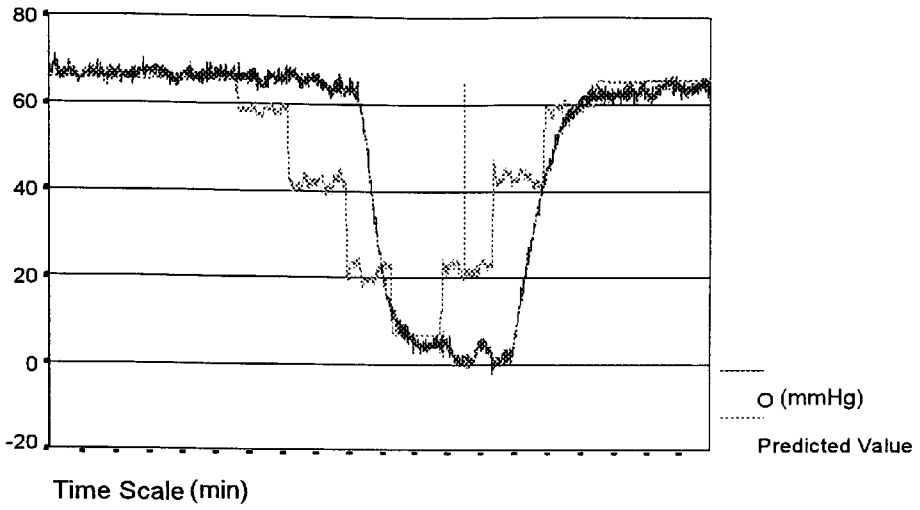


Figure 5-8: Predicted variable for $o(t)$ and original $o(t)$ for the participant GUI032

$$o_{predicted}(t) = o(t-1) + a * o(t-2)^2 * p(t-1) + b * p(t)^2 + c * o(t-2) * p(t)^2 + ...$$

A typical example with the young male participant LES015 was considered. The results from the regression analysis are presented in Figures 5-9 and 5-10.

Multiple R	.99980	Analysis of Variance			
R Square	.99961		DF	Sum of Squares	Mean Square
Adjusted R Square	.99961	Regression	18	1567870.25341	87103.90297
Standard Error	.53977	Residual	2104	613.00837	.29135
		F = 298962.65845		Signif F = .0000	

---------- Variables in the Equation ----------

Variable	B	SE B	Beta	T	Sig T
o_12	.008572	3.4462E-04	.637700	24.875	.0000
o_14	-1.29096E-07	3.7966E-08	-.050635	-3.400	.0007
o_2	.677620	.014317	.677487	47.331	.0000
o_24	-4.86320E-07	1.5935E-08	-.190530	-30.519	.0000
P2	-.002032	1.4353E-04	-.235839	-14.154	.0000
P4	1.16039E-07	1.0498E-08	.126928	11.053	.0000
p_130_12	-8.28982E-09	8.0760E-10	-.150688	-10.265	.0000
p_130_14	1.58931E-12	1.6643E-13	.107327	9.550	.0000
p_1o_1	.004555	1.8049E-04	.257286	25.236	.0000
p_1o_14	-6.61396E-09	4.5151E-10	-.099661	-14.649	.0000
p_2	.189040	.015054	.227616	12.557	.0000
p_220_2	2.66390E-05	2.4647E-06	.108991	10.808	.0000
p_24	-5.59942E-08	7.5242E-09	-.062214	-7.442	.0000
p_240_2	-4.23513E-09	2.8901E-10	-.118952	-14.654	.0000
p_240_22	1.39488E-10	1.1325E-11	.199595	12.317	.0000
p_240_24	-1.63087E-14	1.9500E-15	-.083660	-8.363	.0000
p_20_22	-1.38663E-04	6.2995E-06	-.495509	-22.012	.0000
p_20_24	1.38819E-08	7.8228E-10	.209120	17.745	.0000
(Constant)	-4.615454	.553280		-8.342	.0000

Figure 5-9: Linear regression results for the participant LES015 obtained using SPSS

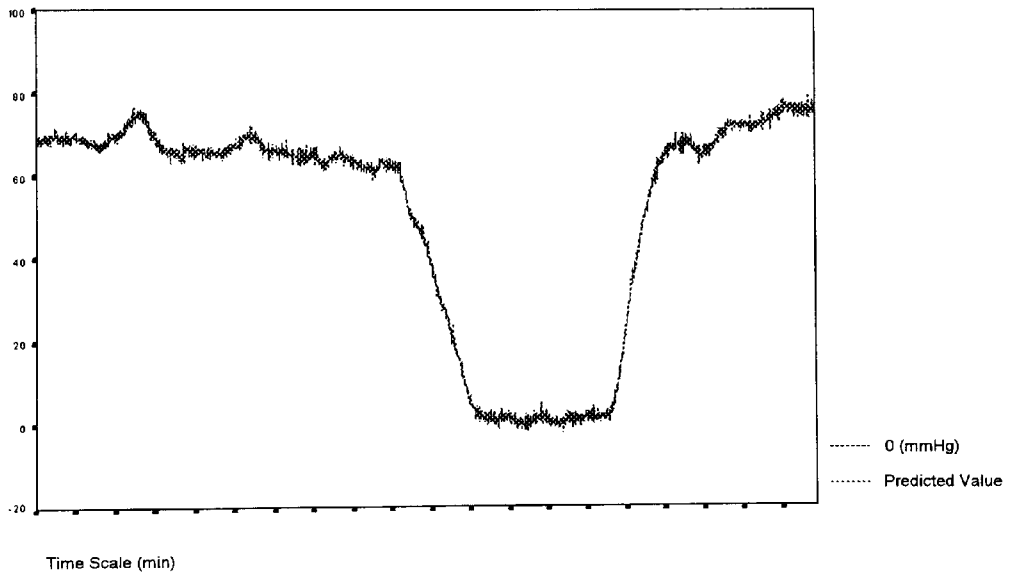


Figure 5-10: Predicted variable for o and original o for the participant LES015

The results show that o was expressed as a polynomial of p and time delayed values of o. Such a high R square value was expected because of the large number of variables included in the regression analysis. It was noticed that the power 4 played an important role in the expression for o. It is essential to notice that powers above 4 were identified as insignificant. This was true for all subjects. It was therefore concluded that a model in terms of power 4 will be appropriate.

The resulting equations were subject specific. Although there was a common pattern in the polynomial structure for each subject; no clear visible pattern between the resulting coefficients was observed.

5.5 Modelling options

As part of the modelling process, it was necessary to determine this pattern in terms of the subject's characteristics. Moreover the equations obtained in the previous section contained too many variables, leading to a complex system of equation which was not operationaly simple to implement in practice for decision. Therefore it was essential to reduce the number of variables, in order to determine a simpler expression. There are two possible options to complete this reduction which are reduction using differential calculus or reduction using stationarity.

5.5.1 Reduction using differential calculus

One way of reducing using differential calculus is by using Taylor series. In particular, for a function defined as follows:

$$x = x(t)$$

then:

$$x(t) = x(t_0) + (t - t_0) * x'(t_0) + \frac{(t - t_0)^2}{2!} * x''(t_0) + ... \tag{5.1}$$

and so:

$$x(t + h) = x(t) + h\frac{dx}{dt} + \frac{h^2}{2}\frac{d^2x}{dt^2} + order(h^3) \tag{5.2}$$

$$x(t-h) = x(t) - h\frac{dx}{dt} + \frac{h^2}{2}\frac{d^2x}{dt^2} + order(h^3) \tag{5.3}$$

Using the notation of the thesis, the equations 5.2 and 5.3 may be written in the form:

$$x(t+1) = x + x' + \frac{1}{2}x'' + order(h^3) \text{ or } x(t-1) = x - x' + \frac{1}{2}x'' + order(h^3) \tag{5.4}$$

where x' and x'' indicate derivatives with respect to t.

From the results at Figure 5-9 for subject LES015, the modelling equation for $o(t)$ has the form:

$$\begin{aligned} o(t) \;=\; & \alpha * o(t-1)^2 + \beta * o(t-1)^4 + \gamma * o(t-2) + \delta * o(t-2)^4 + \epsilon * p(t)^2 + \varepsilon * p(t)^4 \\ & + \zeta * p(t-1)^3 * o(t-1)^2 + \eta * p(t-1)^3 * o(t-1)^4 + \theta * p(t-1) * o(t-1) \\ & + \vartheta * p(t-1) * o(t-1)^4 + \iota * p(t-2) + \kappa * p(t-2)^2 * o(t-2) + \lambda * p(t-2)^4 \\ & + \mu * p(t-2)^4 * o(t-2) + \nu * p(t-2)^4 * o(t-2)^2 + \xi * p(t-2)^4 * o(t-2)^4 \\ & + \pi * p(t-2) * o(t-2)^2 + \varpi * p(t-2) * o(t-2)^4 + \rho \end{aligned}$$

where the coefficents are also presented in Figure 5-9. This can also be written as:

$$\begin{aligned} o(t+1) \;=\; & \alpha * o(t)^2 + \beta * o(t)^4 + \gamma * o(t-1) + \delta * o(t-1)^4 + \epsilon * p(t+1)^2 + \varepsilon * p(t+1)^4 \\ & + \zeta * p(t)^3 * o(t)^2 + \eta * p(t)^3 * o(t)^4 + \theta * p(t) * o(t) \\ & + \vartheta * p(t) * o(t)^4 + \iota * p(t-1) + \kappa * p(t-1)^2 * o(t-1) + \lambda * p(t-1)^4 \\ & + \mu * p(t-1)^4 * o(t-1) + \nu * p(t-1)^4 * o(t-1)^2 + \xi * p(t-1)^4 * o(t-1)^4 \\ & + \pi * p(t-1) * o(t-1)^2 + \varpi * p(t-1) * o(t-1)^4 + \rho \end{aligned}$$

Using the equations 5.4, this becomes:

$$
\begin{aligned}
o+o'+\frac{1}{2}o'' \;=\; & \alpha * o^2+\beta * o^4+\gamma * \left[o-o'+\frac{1}{2}o''\right]+\delta * \left[o-o'+\frac{1}{2}o''\right]^4 \\
& +\epsilon * \left[p+p'+\frac{1}{2}p''\right]^2+\varepsilon * \left[p+p'+\frac{1}{2}p''\right]^4 \\
& +\zeta * p^3 * o^2+\eta * p^3 * o^4+\theta * p * o+\vartheta * p * o^4 \\
& +\iota * \left[p-p'+\frac{1}{2}p''\right]+\kappa * \left[p-p'+\frac{1}{2}p''\right]^2 * \left[o-o'+\frac{1}{2}o''\right] \\
& +\lambda * \left[p-p'+\frac{1}{2}p''\right]^4+\mu * \left[p-p'+\frac{1}{2}p''\right]^4 * \left[o-o'+\frac{1}{2}o''\right] \\
& +\nu * \left[p-p'+\frac{1}{2}p''\right]^4 * \left[o-o'+\frac{1}{2}o''\right]^2 \\
& +\xi * \left[p-p'+\frac{1}{2}p''\right]^4 * \left[o-o'+\frac{1}{2}o''\right]^4 \\
& +\pi * \left[p-p'+\frac{1}{2}p''\right] * \left[o-o'+\frac{1}{2}o''\right]^2 \\
& +\varpi * \left[p-p'+\frac{1}{2}p''\right] * \left[o-o'+\frac{1}{2}o''\right]^4+\rho
\end{aligned}
$$

The analysis was completed and it showed that the transformation did not lead to a reduction. The resulting equation was far too complex for practical use.

It was noticed in this trial that it would have been easier if the combinations were between terms at the same lag order: $o(t-1)*p(t-1)$, $o(t-2)^4*p(t-2)$ and not $p(t-2)^4*o(t-1)$ for instance. Therefore further analyses in steady state conditions will consider this comment. Only combinations lagged at the same order will be included in the future.

5.5.2 Reduction using stationarity

The aim here is to reduce the number of variables involved in the model. It was therefore essential to examine whether terms such as $p(t-1)$ and $p(t)$; $o(t-1)$ and $o(t)$ were related. Following examination of the data, it was found that:

$$
o(t)=\Gamma * o(t-1)+e_1(t)\ ,\ p(t)=\Delta * p(t-1)+e_2(t) \tag{5.5}
$$

Both Γ and Δ values were very close to 1. The results are presented in Figures 5-11 and 5-12.

```
Multiple R            .99774        Analysis of Variance
R Square              .99548                        DF       Sum of Squares      Mean Square
Adjusted R Square     .99548        Regression       1          947347.28281     947347.28281
Standard Error       1.39616        Residual      2206            4300.05452          1.94925

                                    F =  486005.02560       Signif F =  .0000

---------- Variables in the Equation ----------

Variable            B         SE B       Beta          T        Sig T

O_1              .997590      .001431     .997738    697.141     .0000
(Constant)       .118975      .078919                  1.508     .1318
```

Figure 5-11: Regression of o in terms of $o(t-1)$

```
Multiple R            .99914        Analysis of Variance
R Square              .99828                        DF       Sum of Squares      Mean Square
Adjusted R Square     .99828        Regression       1         2670566.78386    2670566.78386
Standard Error       1.44433        Residual      2206            4601.88196          2.08608

                                    F =  1280187.18688      Signif F =  .0000

---------- Variables in the Equation ----------

Variable            B         SE B       Beta          T        Sig T

P_1              .999156   8.8307E-04     .999140   1131.454     .0000
(Constant)       .031657      .045513                   .696     .486
```

Figure 5-12: Regression of p in terms of $p(t-1)$

Since both coefficients were very close to 1, stationarity was indicated. Substituting the relations 5.5, the modelling equations have the form:

$$\Psi_i(o,p) = error$$

with $i = 1, ..., n$ ($n = 28$ is the number of the participants in the present study).

For the subject LES015 considered in the previous section, the polynomial becomes:

$$\begin{aligned} o(t) \;=\; & \alpha * o(t)^2 + \beta * o(t)^4 + \gamma * o(t) + \delta * o(t)^4 + \epsilon * p(t)^2 + \varepsilon * p(t)^4 \\ & + \zeta * p(t)^3 * o(t)^2 + \eta * p(t)^3 * o(t)^4 + \theta * p(t) * o(t) \\ & + \vartheta * p(t) * o(t)^4 + \iota * p(t) + \kappa * p(t)^2 * o(t) + \lambda * p(t)^4 \\ & + \mu * p(t)^4 * o(t) + \nu * p(t)^4 * o(t)^2 + \xi * p(t)^4 * o(t)^4 \\ & + \pi * p(t) * o(t)^2 + \varpi * p(t) * o(t)^4 + \rho \end{aligned}$$

which can be simplified to:

$$
\begin{aligned}
&(\gamma - 1) * o(t) + \alpha * o(t)^2 + (\beta + \delta) * o(t)^4 + \epsilon * p(t)^2 + (\varepsilon + \lambda) * p(t)^4 \\
&+\zeta * p(t)^3 * o(t)^2 + \eta * p(t)^3 * o(t)^4 + \theta * p(t) * o(t) \\
&+ (\vartheta + \varpi) * p(t) * o(t)^4 + \iota * p(t) + \kappa * p(t)^2 * o(t) \\
&+\mu * p(t)^4 * o(t) + \nu * p(t)^4 * o(t)^2 + \xi * p(t)^4 * o(t)^4 \\
&+\pi * p(t) * o(t)^2 + \rho = 0
\end{aligned}
$$

The variability of the coefficients for various subjects is presented later in section 5.6. It was noticed that values of individual coefficients often differ by several higher magnitude. These differences can be the cause of instability in the mathematical modelling and misinterpretation. One way of removing the variation is to rescale the variables. The following scaling procedure was chosen:

$$X(t) = \frac{o(t)}{o(t_0)}$$

with $o(t_0)$ representing the level of oxygen of the participant in the basal conditions ($t = 0$).

$$Y(t) = \frac{p(t)}{\overline{P\max}}$$

with $\overline{Pmax} = 87$ mmHg for young subjects and $\overline{Pmax} = 105$ mmHg for elderly subjects.

These two variables have been used to rewrite the above particular case. LES015 is a young participant, therefore:

$$p(t) = 87 * Y(t)$$

and his oxygen level in resting conditions was 68.8 mmHg, thus:

$$o(t) = 68.8 * X(t)$$

After the above transformation, the following relation was obtained:

$$
\begin{aligned}
&(\gamma-1)*(68.8*X(t))+\alpha*(68.8*X(t))^2+(\beta+\delta)*(68.8*X(t))^4\\
&+\epsilon*(87*Y(t))^2+(\varepsilon+\lambda)*(87*Y(t))^4+\zeta*(87*Y(t))^3*(68.8*X(t))^2\\
&+\eta*(87*Y(t))^3*(68.8*X(t))^4+\theta*(87*Y(t))*(68.8*X(t))\\
&+(\vartheta+\varpi)*(87*Y(t))*(68.8*X(t))^4+\iota*(87*Y(t))+\kappa*(87*Y(t))^2*(68.8*X(t))\\
&+\mu*(87*Y(t))^4*(68.8*X(t))+\nu*(87*Y(t))^4*(68.8*X(t))^2\\
&+\xi*(87*Y(t))^4*(68.8*X(t))^4+\pi*(87*Y(t))*(68.8*X(t))^2+\rho=0
\end{aligned}
$$

Using the numerical values of the coefficients obtained from the regression analysis that is presented in Figure 5-9, the approximated numerical equation after simplification is as follows:

$$
\begin{aligned}
&\left(13.8-14.2Y-23.5Y^3+20.9Y^4\right)X^4+(-37.9+57.2Y+25.8Y^3-37.7Y^4)X^2 \quad (5.6)\\
&+(22.0-29.9Y-13.9Y^2+16.7Y^4)X+4.6-16.6Y+15.1Y^2-3.4Y^4=0
\end{aligned}
$$

where $X \equiv X(t)$ and $Y \equiv Y(t)$ to reduce the size of the equation.

5.5.3 Further examples of reduction using stationarity

In addition to the young male case LES015, further examples of the analysis are new generated. The cases of one young female, one elderly male and one elderly female are presented in this section.

The case of a young female

In the case of GUI021, the analysis lead to an equation for $o(t)$ using the results of the regression analysis. The regression coefficients are initially substituted by Greek letters but they will be given numerical values later. This was to limit the size of the following equations. The

expression for $o(t)$ for GUI021 was initially:

$$\begin{aligned} o(t) &= \alpha * o(t-1)^2 + \beta * o(t-1)^4 + \gamma * o(t-2) + \delta * o(t-2)^4 + \epsilon * p(t-1)^2 \\ &+\varepsilon * p(t-1)^2 * o(t-1)^2 + \zeta * p(t-1)^2 * o(t-1)^4 + \eta * p(t-1)^4 \\ &+\theta * p(t-1)^4 * o(t-1) + \vartheta * p(t-1) * o(t-1) + \iota * p(t-1) * o(t-1)^4 \\ &+\kappa * p(t-2)^2 * o(t-2) + \lambda * p(t-2)^2 * o(t-2)^4 + \mu * p(t-2)^4 * o(t-2) \\ &+\nu * p(t-2)^4 * o(t-2)^4 + \xi * p(t-2) * o(t-2)^2 \\ &+\pi * p(t-2) * o(t-2)^4 + \varpi \end{aligned}$$

The statistics related to this regression are presented below:

Multiple R	0.99987		
R Square	0.99974		
Adjusted R Square	0.99974		
Standard Error	0.29744		
Analysis of Variance			
	DF	Sum of Squares	Mean Square
Regression	17	596783.41379	35104.90669
Residual	1758	155.53093	0.08847
F=396798.39930	Signif F=	0.0000	

Using stationarity, the above equation can be simplified to become:

$$\begin{aligned} o(t) &= \alpha * o(t)^2 + \beta * o(t)^4 + \gamma * o(t) + \delta * o(t)^4 + \epsilon * p(t)^2 \\ &+\varepsilon * p(t)^2 * o(t)^2 + \zeta * p(t)^2 * o(t)^4 + \eta * p(t)^4 \\ &+\theta * p(t)^4 * o(t) + \vartheta * p(t) * o(t) + \iota * p(t) * o(t)^4 \\ &+\kappa * p(t)^2 * o(t) + \lambda * p(t)^2 * o(t)^4 + \mu * p(t)^4 * o(t) \\ &+\nu * p(\quad o(t)^4 + \xi * p(t) * o(t)^2 \\ &+\pi \quad o(t)^4 + \varpi \end{aligned}$$

ect is numerically defined below:

$$p(t) = 87 * Y(t) \text{ and } o(t) = 78.2 * X(t)$$

The quartic equation corresponding to this subject is as follows:

$$\begin{aligned}&\left(-28.9 * Y^4 - 3.9 * Y^2 - 8.0 * Y + 23.3\right) * X^4 + \left(62.6 * Y^2 + 43.3 * Y - 73.4\right) * X^2 \\ &+\left(29.9 * Y^4 - 76.3 * Y^2 - 34.0 * Y + 63.1\right) * X - 12.8 * Y^4 + 26.5 * Y^2 - 11.3 = 0\end{aligned}$$

where $X \equiv X(t)$ and $Y \equiv Y(t)$ to reduce the size of the equation.

The case of an elderly male

The expression for $o(t)$ for GUI032 was initially:

$$\begin{aligned}o(t) \;=\; &\alpha * o(t-1) + \beta * o(t-1)^4 + \gamma * p(t-1)^2 * o(t-1)^4 + \delta * p(t-1)^3 * o(t-1)^2 \\ &+\epsilon * p(t-1)^4 * o(t-1)^4 + \varepsilon * p(t-1) * o(t-1) + \zeta * p(t-1) * o(t-1)^4 \\ &+\eta * p(t-2)^2 + \theta * p(t-2)^2 * o(t-2) + \vartheta * p(t-2)^2 * o(t-2)^3 \\ &+\iota * p(t-2)^3 * o(t-2)^4 + \kappa * p(t-2)^4 + \lambda * p(t-2)^4 * o(t-2) \\ &+\mu * p(t-2)^4 * o(t-2)^2 + \nu * p(t-2)^4 * o(t-2)^4 + \xi * p(t-2) * o(t-2)^2 \\ &+\pi * p(t-2) * o(t-2)^4 + \varpi\end{aligned}$$

The statistics related to this regression are presented below:

Multiple R	0.99977		
R Square	0.99954		
Adjusted R Square	0.99954		
Standard Error	0.53265		
Analysis of Variance			
	DF	Sum of Squares	Mean Square
Regression	19	1408051.97582	74107.99873
Residual	2284	648.01393	0.28372
F=261202.20834	signif F=	0.0000	

Using stationarity, the above equation is:

$$
\begin{aligned}
o(t) \;=\; & \alpha * o(t) + \beta * o(t)^4 + \gamma * p(t)^2 * o(t)^4 + \delta * p(t)^3 * o(t)^2 \\
& + \epsilon * p(t)^4 * o(t)^4 + \varepsilon * p(t) * o(t) + \zeta * p(t) * o(t)^4 \\
& + \eta * p(t)^2 + \theta * p(t)^2 * o(t) + \vartheta * p(t)^2 * o(t)^3 \\
& + \iota * p(t)^3 * o(t)^4 + \kappa * p(t)^4 + \lambda * p(t)^4 * o(t) \\
& + \mu * p(t)^4 * o(t)^2 + \nu * p(t)^4 * o(t)^4 + \xi * p(t) * o(t)^2 \\
& + \pi * p(t) * o(t)^4 + \varpi
\end{aligned}
$$

The transformation for this subject is numerically defined below:

$$p(t) = 105 * Y(t) \text{ and } o(t) = 66.9 * X(t)$$

The quartic equation corresponding to this subject is as follows:

$$
\begin{aligned}
& \left(21.1 * Y^4 - 73.7 * Y^3 - 24.6 * Y^2 - 20.9 * Y + 23.3\right) * X^4 + 108.6 * Y^2 * X^3 \\
& + (-114.6 * Y^4 + 80.4 * Y^3 + 47.2 * Y - 71.6) * X^2 \\
& + (92.3 * Y^4 - 95.1 * Y^2 - 26.0 * Y + 50.5) * X - 9.6 * Y^4 + 11.0 * Y^2 - 3.7 = 0
\end{aligned}
$$

where $X \equiv X(t)$ and $Y \equiv Y(t)$ to reduce the size of the equation.

The case of an elderly female

The expression for $o(t)$ for BEN034 was initially:

$$
\begin{aligned}
o(t) \;=\; & \alpha * o(t-1) + \beta * o(t-1)^4 + \gamma * o(t-2) + \delta * p(t-1)^2 * o(t-1) \\
& + \epsilon * p(t-1)^2 * o(t-1)^4 + \varepsilon * p(t-1)^3 * o(t-1)^2 + \zeta * p(t-1)^4 * o(t-1) \\
& + \eta * p(t-1)^4 * o(t-1)^2 + \theta * p(t-1) * o(t-1)^2 + \vartheta * p(t-1) * o(t-1)^4 \\
& + \iota * p(t-2)^2 + \kappa * p(t-2)^4 + \lambda * p(t-2)^4 * o(t-2)^2 \\
& + \mu * p(t-2)^4 * o(t-2)^4 + \nu * p(t-2) * o(t-2) + \xi * p(t-2) * o(t-2)^4 \\
& + \varpi
\end{aligned}
$$

The statistics related to this regression are presented below:

Multiple R	0.99982		
R Square	0.99965		
Adjusted R Square	0.99964		
Standard Error	0.45406		
Analysis of Variance			
	DF	Sum of Squares	Mean Square
Regression	18	1500981.19157	83387.84398
Residual	2582	532.33758	0.20617
F=404456.53678	Signif F=	0.0000	

Using stationarity, the above equation becomes:

$$\begin{aligned} o(t) &= \alpha * o(t) + \beta * o(t)^4 + \gamma * o(t) + \delta * p(t)^2 * o(t) \\ &+\epsilon * p(t)^2 * o(t)^4 + \varepsilon * p(t)^3 * o(t)^2 + \zeta * p(t)^4 * o(t) \\ &+\eta * p(t)^4 * o(t)^2 + \theta * p(t) * o(t)^2 + \vartheta * p(t) * o(t)^4 \\ &+\iota * p(t)^2 + \kappa * p(t)^4 + \lambda * p(t)^4 * o(t)^2 \\ &+\mu * p(t)^4 * o(t)^4 + \nu * p(t) * o(t) + \xi * p(t) * o(t)^4 + \varpi \end{aligned}$$

The transformation for this subject is numerically defined below:

$$p(t) = 105 * Y(t) \text{ and } o(t) = 65.9 * X(t)$$

The quartic equation corresponding to this subject is as follows:

$$\begin{aligned} &(-21.8 * Y^4 + 32.4 * Y^2 - 37.9 * Y + 20.4) * X^4 + (-22.3 * Y^4 + 25.2 * Y^3 + 55.6 * Y - 59.9) * X^2 \\ &+(31.6 * Y^4 - 49.7 * Y^2 - 23.4 * Y + 43.0) * X - 3.3 * Y^4 + 6.8 * Y^2 - 3.4 = 0 \end{aligned}$$

where $X \equiv X(t)$ and $Y \equiv Y(t)$ to reduce the size of the equation.

5.5.4 Model selection, standardisation and interpretation

The equation 5.6 after simplification for LES015 was:

$$\left(20.9Y^4 - 23.5Y^3 - 14.2Y + 13.8\right) * X^4 + \left(-37.7Y^4 + 25.8Y^3 + 57.2Y - 37.9\right) * X^2$$
$$+\left(16.7Y^4 - 13.9Y^2 - 29.9Y + 22.0\right) * X - 3.4Y^4 + 15.1Y^2 - 16.6Y + 4.6 = 0$$

where $X \equiv X(t)$ and $Y \equiv Y(t)$ to reduce the size of the equation.

In order to interpret model optimality, it is necessary to determine where the critical turning points arise. This was achieved by differentiating the above relation with respect to X to obtain:

$$\left(20.9Y^4 - 23.5Y^3 - 14.2Y + 13.8\right) * 4X^3 + \left(-37.7Y^4 + 25.8Y^3 + 57.2Y - 37.9\right) * 2X$$
$$+\left(16.7Y^4 - 13.9Y^2 - 29.9Y + 22.0\right) = 0$$

which can be written as follows:

$$X^3 + A(Y)X + B(Y) = 0 \tag{5.7}$$

where:

$$A(Y) = \frac{2(57.2Y - 37.7Y^4 + 25.8Y^3 - 37.9)}{4\left(13.8 - 14.2Y + 20.9Y^4 - 23.5Y^3\right)}$$

$$B(Y) = \frac{16.7Y^4 - 13.9Y^2 - 29.9Y + 22.0}{4\left(13.8 - 14.2Y + 20.9Y^4 - 23.5Y^3\right)}$$

Using the power series approximations, about $Y = 0$, the above expressions can be simplified as follows:

$$A(Y) = -1.3732 + .65947Y + O\left(Y^2\right)$$

and

$$B(Y) = .39855 - .13156Y + O\left(Y^2\right)$$

and lead to the following equation for LES015:

$$X^3 + (0.66Y - 1.37)X + (0.40 - 0.13Y) = 0$$

where the terms $O\left(Y^2\right)$ have been ignored.

Clearly this type of approximation will be valid only for small values of Y, and so is not appropriate for use across the entire range $0 \leqslant Y \leqslant 1$. In addition other Taylor approximations could be developed which would be valid near particular values of Y. This is not a satisfactory and reliable approach to the problem of linearisation for all valid Y, and so direct parameterisation of:

$$X^3 + (\alpha Y - \beta)X + (\delta - \gamma Y) = 0 \tag{5.8}$$

from the original data was considered. The coefficients calculated for each subject are presented in Table 5.2.

It is interesting to note that the estimated parameters α, β, γ and δ were all found significant in the relation and consistent with the obtained functional form state above. Using Table 5.2, a general equation for both males and females (using the average value for each parameter) can be written as:

For males

$$X^3 + (2.33Y - 2.90)X + (1.85 - 2.04Y) = 0$$

For females

$$X^3 + (2.43Y - 3.07)X + (2.00 - 2.09Y) = 0$$

The observed variability between the calculated values α, β, γ and δ can be attributed to subjects characteristics. The relationship between the coefficients and the personal characteristics was evaluated separately for males and females. So far in the modelling process, subject's characteristics (age, sex, weight, height) have not been explicitly discussed. It is natural to explain the variability of α, β, γ and δ between subjects in terms of their case specific characteristics.

A regression analysis was performed and the following relationships resulted:

Subjects	sex	group	α	β	δ	γ
1	m	1	1.99	2.10	1.06	1.34
2	m	1	1.36	2.09	1.00	0.99
3	m	1	3.54	3.95	2.88	3.28
4	m	1	1.81	2.33	1.30	1.56
5	m	1	1.58	2.13	1.13	1.36
6	m	1	1.71	2.38	1.33	1.31
7	m	1	4.01	4.98	3.96	4.77
8	m	1	2.31	3.41	2.31	2.30
9	m	2	3.32	3.45	2.34	2.06
10	m	2	3.49	3.92	2.86	3.32
11	m	2	1.53	2.22	1.20	1.45
12	m	2	1.77	2.50	1.49	1.43
13	m	2	1.89	2.21	1.22	1.39
14	f	1	1.65	2.33	1.26	1.23
15	f	1	4.79	6.45	5.71	5.12
16	f	1	1.82	2.37	1.37	1.39
17	f	1	1.40	1.33	0.43	0.57
18	f	1	2.00	2.21	1.20	1.51
19	f	1	2.85	3.22	2.17	2.71
20	f	1	2.48	3.45	2.21	2.24
21	f	1	1.24	1.63	0.64	0.78
22	f	1	2.48	2.87	1.81	2.01
23	f	2	2.92	4.00	2.16	1.84
24	f	2	1.01	2.40	1.32	1.05
25	f	2	2.81	2.98	1.85	2.22
26	f	2	3.74	4.13	3.09	3.65
27	f	2	3.86	4.58	3.60	3.87
28	f	2	1.45	2.15	1.16	1.14

Table 5.2: Table of the coefficients α, β, γ and δ calculated individually for all subjects

For males

$$\begin{aligned}
\alpha &= 0.98\beta - 3.79va_0 + 0.19 \\
\beta &= 0.02age + 0.06weight - 0.12c_0 - 0.04o_0 + 8.91va_0 + 17.51vv_0 + 1.44 \\
\gamma &= 1.14\delta + 0.01height - 2.54 \\
\delta &= 0.99\beta - 1.01
\end{aligned}$$

The respective R square values for α, β, γ and δ are: 0.93, 0.79, 0.96 and 0.99 respectively.

For females

$$\begin{aligned}
\alpha &= 0.77\beta - 1.42va_0 + 0.36 \\
\beta &= 0.07age + 0.10height + 0.48c_0 + 0.06o_0 + 33.36va_0 - 25.46vv_0 - 42.39 \\
\gamma &= 0.91\delta - 0.01weight + 0.95 \\
\delta &= 0.99\beta - 1.07
\end{aligned}$$

The respective R square values for α, β, γ and δ are: 0.90, 0.75, 0.95 and 0.97 respectively.

The predicted values (denoted α', β', γ' and δ') using similar equations with the exact coefficients are reported in Table 5.3.

It can be noticed that the value of R square in determining the coefficient β is comparatively low. In addition, the parametrs α, γ and δ are all expressed in terms of β. It was therefore crucial to check the validity of this model. To emphasise the differences between the actual values of β and its predictive values, both sets of values were reported in the same graph for both males and females in Figure 5-13.

Some discrepancies in this first candidate model occurred which are highlighted in Figure 5-13. It was clear that the fit was not satisfactory. It was therefore essential to improve the present model by considering alternative quartic relationships. One such alternative is:

$$X(t)^4 + AY(t)X(t)^2 + BX(t) + C = error(t) \tag{5.9}$$

Subjects	sex	group	α	α'	β	β'	δ	δ'	γ	γ'
1	m	1	1.99	1.79	2.10	2.45	1.06	1.06	1.34	1.26
2	m	1	1.36	1.67	2.09	2.56	1.00	1.05	0.99	1.04
3	m	1	3.54	3.38	3.95	3.70	2.88	2.89	3.28	3.25
4	m	1	1.81	1.75	2.33	2.77	1.30	1.29	1.56	1.44
5	m	1	1.58	1.52	2.13	1.70	1.13	1.09	1.36	1.27
6	m	1	1.71	1.73	2.38	1.98	1.33	1.34	1.31	1.50
7	m	1	4.01	4.12	4.98	4.96	3.96	3.91	4.77	4.59
8	m	1	2.31	2.58	3.41	3.06	2.31	2.36	2.30	2.69
9	m	2	3.32	3.04	3.45	3.01	2.34	2.40	2.06	2.45
10	m	2	3.49	3.46	3.92	3.52	2.86	2.86	3.32	3.11
11	m	2	1.53	1.80	2.22	2.35	1.20	1.18	1.45	1.16
12	m	2	1.77	2.03	2.50	2.54	1.49	1.46	1.43	1.48
13	m	2	1.89	1.45	2.21	3.08	1.22	1.17	1.39	1.33
14	f	1	1.65	1.64	2.33	1.74	1.26	1.26	1.23	1.52
15	f	1	4.79	4.92	6.45	5.80	5.71	5.37	5.12	5.49
16	f	1	1.82	1.82	2.37	2.59	1.37	1.30	1.39	1.41
17	f	1	1.40	1.10	1.33	1.50	0.43	0.26	0.57	0.52
18	f	1	2.00	1.81	2.21	3.20	1.20	1.14	1.51	1.30
19	f	1	2.85	2.73	3.22	3.15	2.17	2.14	2.71	2.40
20	f	1	2.48	2.59	3.45	4.13	2.21	2.37	2.24	2.37
21	f	1	1.24	1.26	1.63	1.73	0.64	0.56	0.78	0.77
22	f	1	2.48	2.16	2.87	2.18	1.81	1.80	2.01	2.01
23	f	2	2.92	3.23	4.00	3.97	2.16	2.92	1.84	2.24
24	f	2	1.01	2.01	2.40	2.19	1.32	1.33	1.05	1.45
25	f	2	2.81	2.43	2.98	3.02	1.85	1.91	2.22	1.91
26	f	2	3.74	3.40	4.13	3.66	3.09	3.05	3.65	3.17
27	f	2	3.86	3.70	4.58	3.66	3.60	3.50	3.87	3.50
28	f	2	1.45	1.72	2.15	3.58	1.16	1.08	1.14	1.27

Table 5.3: Comparison between calculated and predicted values for the coefficients α, β, γ and δ for all subjects

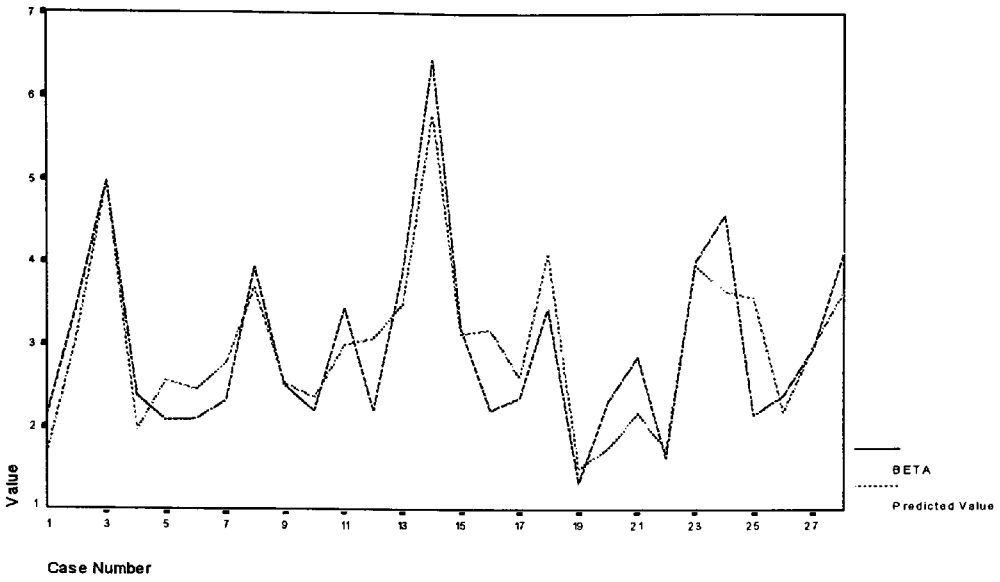


Figure 5-13: Comparison between real coefficients and predicted values of β for both males and females

In order to interpret this model's optimality, it was necessary to determine where the critical turning points arise. This was achieved by differentiating the relation 5.9 with respect to X to obtain:

$$X(t)^3 + aY(t)X(t) + b = 0 \tag{5.10}$$

where a and b are coefficients which were calculated individually for each subject using regression analysis based on the equation 5.10.

The general functional form 5.10 that was obtained for all subjects, is of the form which often occurs in Catastrophe Theory. A review of this theory is the subject of appendix G. Clearly the final modelling equations, if there is any, should have an identical form for all subjects and so it is necessary to establish a common pattern. The quartic relation in X, coupled with the sudden changes in scaled oxygen (X) which occur in the data at about $Y = 0.8$, naturally enabled models based upon catastrophe theory to be considered.

For LES015 that has been considered throughout the chapter, the regression analysis pro-

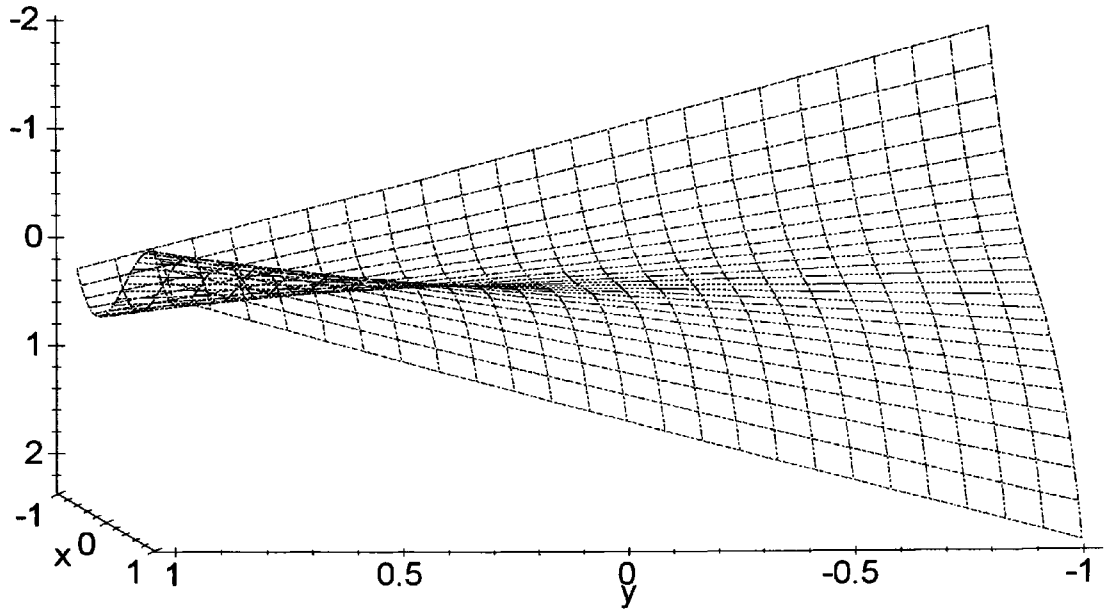


Figure 5-14: Surface for one specific subject with extensions of the axes

vided $a = -1.09$ and $b = 0.12$. The results are presented in Table 5.4. In addition the particular surface

$$Z(X, Y) = X(t)^3 + aY(t)X(t) + b$$

for the case $a = -1.09$ and $b = 0.12$ is presented in Figure 5-14.

Here the X and Y axes represent the variation of $X(t)$ and $Y(t)$ respectively. The vertical axis is $Z(X, Y)$ as defined above. Clearly the surface shown highlights a cusp which is often seen in standard catastrophy theory. In terms of the physical problem, the graph shows that if the scaled splint pressure is increased from 0 to 1 then a cusp will occur. In particular for values of $Y(t)$ greater than a threshold of about 0.4 the splint pressure can be potentially dangerous. This can be seen from the critical values (or cusp) shown on the graph.

5.6 Final interpretation

The a and b were of the same sign, ranged in a restricted interval which meant that there are high degree of consistency between subjects. In general terms, we had

$$\begin{aligned} -1.91 &< a < -0.99 \text{ and } 0.10 < b < 0.57 \text{ for males} \\ -1.57 &< a < -1.01 \text{ and } 0.18 < b < 0.33 \text{ for females} \end{aligned}$$

As for the previous model, the observed variability between the calculated values a and b can be attributed to subjects characteristics. The relationship between the coefficients and the personal characteristics was evaluated separately for males and females. It is natural to explain the variability of a and b between subjects in terms of their case specific characteristics.

The differences in a and b values have to be taken into account in the modelling. In order to observe the corresponding general characteristics, all the values are reported in Table 5.4. This table shows the individual values for a and b with respect to their individual characteristics, and the resting single value for the measured parameters.

A close examination of the a and b values suggested a classification of two groups according to sex. Analysis for males and females were performed independently. Therefore the general equations can be written using the mean values as follows:

For males

$$X(t)^3 - 1.13Y(t)X(t) + 0.22 = 0$$

For females

$$X(t)^3 - 1.25Y(t)X(t) + 0.23 = 0$$

Regression analysis was conducted for each group to express a and b in terms of age, weight and height. The results of the analyses are shown in Figures 5-15, 5-16, 5-17 and 5-18.

For both groups, it was interesting to note that a is a function of resting conditions vascular levels, whereas b is a function of more general characteristics. It could also be noticed that

Subjects	sex	group	a	b	age	weight	height	o_0	c_0	va_0	vv_0
1	m	1	-0.99	0.26	23	65	180	40.2	37.0	0.12	0.08
2	m	1	-1.09	0.12	25	79	169	68.8	39.3	0.15	0.10
3	m	1	-1.27	0.25	23	82	174	80.6	41.0	0.18	0.18
4	m	1	-1.10	0.15	24	70	173	77.2	53.7	0.19	0.24
5	m	1	-1.00	0.10	24	62	175	90.8	32.4	0.20	0.09
6	m	1	-1.02	0.15	25	67	175	91.2	42.4	0.21	0.15
7	m	1	-1.91	0.40	23	62	182	51.3	42.4	0.25	0.23
8	m	1	-1.09	0.25	28	77	180	60.6	43.4	0.25	0.09
9	m	2	-0.99	0.14	56	65	161	55.1	42.1	0.14	0.13
10	m	2	-1.12	0.16	58	72	166	55.8	45.4	0.15	0.15
11	m	2	-0.99	0.10	58	71	162	66.9	40.6	0.15	0.08
12	m	2	-0.99	0.16	50	75	161	78.5	34.9	0.16	0.07
13	m	2	-1.09	0.57	51	66	172	83.9	37.5	0.24	0.12
14	f	1	-1.19	0.20	20	51	163	68.5	32.7	0.36	0.23
15	f	1	-1.27	0.26	22	59	170	79.2	41.7	0.29	0.21
16	f	1	-1.14	0.30	22	70	160	78.2	37.8	0.26	0.18
17	f	1	-1.34	0.33	22	73	180	50.0	34.9	0.20	0.10
18	f	1	-1.20	0.25	23	66	168	68.8	39.7	0.18	0.10
19	f	1	-1.21	0.19	24	47	163	76.7	44.3	0.08	0.06
20	f	1	-1.57	0.23	24	53	161	59.2	33.8	0.30	0.06
21	f	1	-1.03	0.29	24	68	176	82.5	44.1	0.25	0.40
22	f	1	-1.08	0.18	26	52	165	84.2	29.9	0.29	0.13
23	f	2	-1.01	0.18	50	60	157	65.9	42.3	0.15	0.10
24	f	2	-1.34	0.19	50	62	159	59.2	38.7	0.14	0.08
25	f	2	-1.44	0.22	50	64	150	42.7	46.2	0.16	0.14
26	f	2	-1.27	0.18	53	53	169	62.1	38.4	0.10	0.02
27	f	2	-1.51	0.24	55	65	162	47.9	43.6	0.13	0.10
28	f	2	-1.15	0.24	57	65	163	69.2	38.4	0.21	0.17

Table 5.4: Table of the coefficients a and b calculated individually for all subjects

```
Multiple R           ,93145
R Square             ,86761
Adjusted R Square    ,80141
Standard Error       ,11025

Analysis of Variance
                    DF       Sum of Squares       Mean Square
Regression           4              ,63730            ,15933
Residual             8              ,09725            ,01216

F =       13,10668       Signif F =  ,0014


------------------ Variables in the Equation ------------------

Variable                B         SE B        Beta         T  Sig T

CO2.0            ,030790      ,009117    ,655654     3,377  ,0097
O2.0             ,008163      ,002168    ,527246     3,765  ,0055
VA0            -2,276661      ,839956   -,402048    -2,710  ,0266
VV0            -4,361509      ,889103   -,994219    -4,906  ,0012
(Constant)     -1,960283      ,381364               -5,140  ,0009
```

Figure 5-15: Linear regression analysis of a for males

```
Multiple R           ,93487
R Square             ,87398
Adjusted R Square    ,81797
Standard Error       ,06771

Analysis of Variance
                    DF       Sum of Squares       Mean Square
Regression           4              ,28614            ,07153
Residual             9              ,04126            ,00458

F =       15,60461       Signif F =  ,0004


------------------ Variables in the Equation ------------------

Variable                B         SE B        Beta         T  Sig T

CO2.0           -,021220      ,007075   -,645158    -2,999  ,0150
O2.0             ,007616      ,001684    ,638792     4,523  ,0014
VA0            -1,595715      ,461869   -,842634    -3,455  ,0072
VV0             1,372541      ,361940    ,826697     3,792  ,0043
(Constant)      -,805655      ,360069               -2,238  ,0521
```

Figure 5-16: Linear regression analysis of a for females

```
Multiple R            .91613
R Square              .85284
Adjusted R Square     .81541
Standard Error        .10351

Analysis of Variance
                    DF       Sum of Squares       Mean Square
Regression           2                .11279             .05640
Residual            10                .10715             .01071

F =        5.26365       Signif F =  .0274


------------------ Variables in the Equation ------------------

Variable                B         SE B        Beta          T  Sig T

AGE              .008533      .003286     .978169      2.597  .0266
HEIGHT           .022740      .007010    1.222083      3.244  .0088
(Constant)     -3.991785     1.300450                 -3.070  .0119
```

Figure 5-17: Linear regression analysis of b for males

```
Multiple R            ,91972
R Square              ,84589
Adjusted R Square     ,82020
Standard Error        ,02030

Analysis of Variance
                    DF       Sum of Squares       Mean Square
Regression           2                ,02713             ,01356
Residual            12                ,00494             ,00041

F =       32,93248       Signif F =  ,0000


------------------ Variables in the Equation ------------------

Variable                B         SE B        Beta          T  Sig T

AGE             -,001535  3,6027E-04    -,484925     -4,260  ,0011
WEIGHT           ,005099  7,0022E-04     ,828942      7,282  ,0000
(Constant)      -,023235      ,043362                 -,536  ,6019
```

Figure 5-18: Linear regression analysis of b for females

there were no common variables in the expression of a and b. In other terms, a and b were mutually exclusive. The reasons are still unclear.

It could be noticed that the form of a was precisely the same for both males and females.

For males, the coefficient a was expressed as follows:

$$a = -1.960283 + 0.030790 * c_0 + 0.008163 * o_0 - 2.276661 * va_0 - 4.361509 * vv_0$$

For females, the coefficient a was expressed as follows:

$$a = -0.805655 - 0.021220 * c_0 + 0.007616 * o_0 - 1.595715 * va_0 + 1.372541 * vv_0$$

However a small difference exists in the form of b between males and females. Where instead of height for males, weight for females was significant. This can be due to the sample size and quality even if the reasons are unclear.

For males

$$b = -3.991785 + 0.008533 * age + 0.022740 * height$$

For females

$$b = -0.023235 - 0.001535 * age + 0.005099 * weight$$

A table that compares the coefficients a and b individually calculated in the regression analysis and the predictive values a and b using the modelling equations. This information is presented in Table 5.5.

In general, very close agreement was obtained. Both individually calculated a and b and predicted a and b using the above expressions for males and females are reported in Figures 5-19 and 5-20 respectively.

Subjects	sex	group	a	b	predictive a	predictive b
1	m	1	-0.99	0.26	-1.12	0.30
2	m	1	-1.09	0.12	-0.97	0.06
3	m	1	-1.27	0.25	-1.24	0.16
4	m	1	-1.10	0.15	-1.16	0.15
5	m	1	-1.00	0.10	-1.07	0.19
6	m	1	-1.02	0.15	-1.04	0.20
7	m	1	-1.91	0.40	-1.81	0.34
8	m	1	-1.09	0.25	-1.09	0.34
9	m	2	-0.99	0.14	-1.10	0.15
10	m	2	-1.12	0.16	-1.10	0.28
11	m	2	-0.99	0.10	-0.86	0.19
12	m	2	-0.99	0.16	-0.91	0.10
13	m	2	-1.09	0.57	-1.19	0.35
14	f	1	-1.19	0.20	-1.24	0.21
15	f	1	-1.27	0.26	-1.26	0.24
16	f	1	-1.14	0.30	-1.18	0.30
17	f	1	-1.34	0.33	-1.35	0.32
18	f	1	-1.20	0.25	-1.28	0.28
19	f	1	-1.21	0.19	-1.21	0.18
20	f	1	-1.57	0.23	-1.47	0.21
21	f	1	-1.03	0.29	-0.96	0.29
22	f	1	-1.08	0.18	-1.08	0.20
23	f	2	-1.01	0.18	-1.02	0.21
24	f	2	-1.34	0.19	-1.29	0.22
25	f	2	-1.44	0.22	-1.52	0.23
26	f	2	-1.27	0.18	-1.28	0.17
27	f	2	-1.51	0.24	-1.44	0.22
28	f	2	-1.15	0.24	-1.19	0.22

Table 5.5: Comparison between calculated and predictive values for the coefficients a and b for all subjects

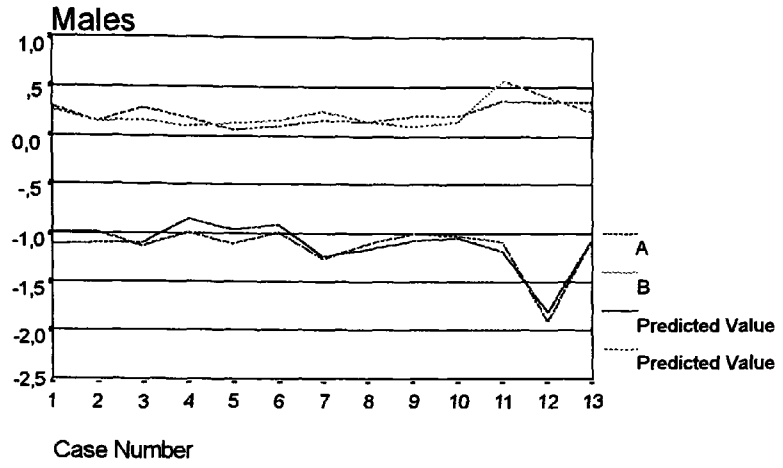


Figure 5-19: Comparison between real coefficients and predicted values for males

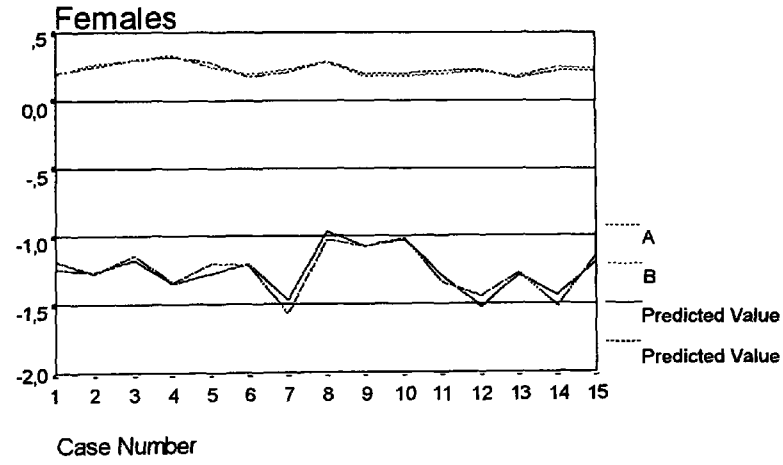


Figure 5-20: Comparison between real coefficients and predicted values for females

5.7 Discussion

The model

$$X(t)^4 + A * Y(t) * X(t)^2 + B * X(t) + C = error(t)$$

that has critical points generated by:

$$X(t)^3 + aY(t) * X(t) + b = 0$$

produced satistifying results. Therefore there was no apparent need at this stage to consider further quartic models. However in future, when non healthy subjects are considered, it may appear that a more general form is needed. In the present model, it is essential to notice that the coefficient a was related to individual vascular level measured in resting conditions, whereas b was related to general characteristics of the subject (age, height or weight), depending on the sex of the subject. Therefore, given the specifications of one person and after a vascular examination at rest, the coefficients a and b can be evaluated and plot the singularities of the quartic relation for this particular subject.

Chapter 6

CONCLUSIONS

6.1 Summary of aims and achievements

The treatment of wounds has been a challenge to those versed in the healing arts. However the requirement for the application of compression bandages is one of the main areas of agreement in the management of wound healing. The required pressure level and the method of its application to provide an optimum treatment is a delicate balance and is controversial. Indeed there are uncertainties on the balance between the apparent beneficial effect on the venous system and the risk of arterial ischaemia resulting from an external uniform compression. Moreover due to the aging of the population, it has been observed that there is an increased prevalence of arterial disease. The understanding of the diagnosis for the correct type of bandage and the variability of application of these bandages is not complete. A clinical analysis based system that will assist with the diagnosis of wound positions on patients and the repeatability of bandage pressures applied to the wound would be useful for day life clinicians. Furthermore the prevention and the treatment of sores are expensive. It follows that a model which is able to determine the required sub-bandage pressure would enhance treatment strategy and hence, vastly reduce the cost spent on sore treatment and bandages each year. Therefore the aim of this study was to determine and evaluate the effects of a positive uniform compression applied to the whole lower limb on the haemodynamics and the distal microcirculation in humans.

The apparent beneficial effect of compression on the venous function is suggested as resulting from an improvement in calf muscle pump function with an increase in venous flow velocity or

reduction in venous reflux. To describe this process, a mathematical model has been produced. The research was completed by means of two separate but linked analyses, conducted under a collaborative agreement. The University Hospital of Angers provided the advice and the equipment needed for the medical development and the University of Glamorgan provided the experience and the facilities to achieve the modelling assessment.

The aim of the first analysis was to design an appropriate experiment to create a database which would allow for experimental analysis. This was necessary since very little information was available in the literature concerning the effect of external compression on venous blood flow in the distal extremities. In addition it was difficult to find results on the effect of uniform compression on arterial blood flow because most recent studies have been performed on the effects of locally applied pressure on the microcirculation. Even less was known regarding the effects of externally applied pressure on both venous and arterial blood flow, and distal microcirculation. The experiments were designed to overcome these difficulties. Both microcirculation and macrocirculation were measured during the experiments in response to externally applied pressure using a standard inflatable splint extending from the ankle to the upper thigh. Three parameters describing microcirculation were recorded throughout the experiments. They were the transcutaneous oxygen and carbon dioxide pressures (denoted by o and c respectively) and laser Doppler flux (denoted by l). Both arterial and venous femoral velocities (respectively denoted by va and vv) were measured by the Doppler ultrasound method to evaluate the effects of compression on macrocirculation. The applied pressure of the splint was also recorded and was denoted by p. General characteristics (such as age, sex, weight, height) were noted during the physical examination to determine whether the subject satisfied the criteria of inclusion. The splint was inflated to 10 mmHg and maintained for three minutes after basal conditions were obtained and measured. During the last two minutes, the femoral velocities were measured. Each step duration was 3 minutes in total. After this first step, the inflation of the splint was increased at 20 mmHg, then successively increased by steps of 20 mmHg. The increase of the splint pressure was ended when no decrease in LDF and tcpO2 was observed between two successive levels of splint pressure. The minimum values were defined as the physiological zero of the participant, observed at the individual maximum reached splint pressure denoted by $P\max$. The pressure of the splint was then released by steps of 20 mmHg, until total deflation

of the splint. Twenty eight healthy Caucasian subjects (17 young volunteers and 11 elderly volunteers) participated in the present study. The findings of the investigation demonstrated a significant impairment of both arterial velocities and laser Doppler flux for all subjects and transcutaneous carbon dioxide pressure for young subjects with compressive value as low as 10 mmHg. A large database was created from these experiments, and as far as we know it was the first time that an experimental protocol was designed to group both macro and microcirculation in response to external uniform pressure applied to the whole lower limb in humans.

In the second analysis, a statistical model, based on experiments, was created to explain the relationships between externally applied compressive forces and resulting vascular effects in human lower limbs. A clinician would find the model easy to use because of subject's personal characteristics can be used to define the model coefficients directly.

In an early stage of the modelling process, the available data sets were classified into different groups. After classifications, two variables (p and o) were used to build the initial model. The remaining variables were used for the final model specification. As the variables were included at different levels of the modelling process, the developed model was of a hierarchical nature. The large volume and extent of the available data presented a challenge. Issues of computer storage, time consumption and difficulty in modelling, the data set had to be addressed. It was therefore logical to consider ways of reducing the sample size. In order to minimise the sample size without loss of significant information, a sampling rate of one observation per second was found to be appropriate for the analysis. Indeed this rate was chosen to give a good balance between the accuracy of the database and the relatively small size of the file related to computer limitations. This reduction had several important implications. Firstly, from an economic point of view, the results suggested that a large increase in the sampling rate does not necessarily improve the correlation between p and o, large increase in the sampling rate caused problem in data management and storage, and instruments for similar purpose could be designed with smaller sampling rate in mind, which may cost less. Secondly, it casts doubt on past research. In previous experiments, it appeared that no particular attention has been paid to sampling rates. Finally, the results indicated that the maximum information content can be achieved with a relatively small sampling rate. Therefore the choice of the sampling rate is crucial for further analysis. Once the optimum sampling rate was chosen, the model development began.

A model expressing o as a polynomial of p (including time delay terms) was produced. This model was further simplified in a search for the identification of a common pattern for different subjects. The modelling equations were considered in a steady state condition. In addition, the model was transformed using the following relations:

$$X(t) = \frac{o(t)}{o(t_0)}$$

with $o(t_0)$ representing the level of oxygen of the participant in the basal conditions ($t = 0$).

$$Y(t) = \frac{p(t)}{\overline{P\max}}$$

with $\overline{P\max} = 87$ mmHg for young subjects and $\overline{P\max} = 105$ mmHg for elderly subjects.

Using the above transformation, the common pattern obtained from individual analysis was used to produce a preliminary model in terms of four parameters α, β, δ and γ. These coefficients were expressed in terms of subject's characteristics. However it was found that this model gave a limited overall performance. This was subsequently refine to produce:

$$X(t)^4 + AY(t)X(t)^2 + BX(t) + C(t) = error(t) \tag{6.1}$$

The set of critical values (singularities) for the transformed oxygen level X are determined from:

$$X(t)^3 + aY(t)X(t) + b = 0 \tag{6.2}$$

where a and b are coefficients calculated individually for each subject. These coefficients were expressed in terms of the remaining variables. The results are summarised below:

For males

$$a = -1.960283 + 0.030790 * c_0 + 0.008163 * o_0 - 2.276661 * va_0 - 4.361509 * vv_0$$

$$b = -3.991785 + 0.008533 * age + 0.022740 * height$$

For females

$$a = -0.805655 - 0.021220 * c_0 + 0.007616 * o_0 - 1.595715 * va_0 + 1.372541 * vv_0$$

$$b = -0.023235 - 0.001535 * age + 0.005099 * weight$$

The developed model was obtained as a result of accommodating both micro and macro information. The first stage of the model was developed using detailed observed data regarding oxygen and pressure, while the second stage consisted of macro information regarding subject's characteristics. Hence the developed model can be used by practitioners as a predictive tool for decision making. Given the information on a specific subject, it is possible to calculate both coefficients a and b and plot the singularities of the quartic relation for this particular subject. This can provide a workable plan for practitioners to control the way in which they can manage the application of pressure bandages for the subject in question.

It should be noted that the application of hierarchical strategy with catastrophy theory is at the forefront of modern mathematics research. To our knowledge, this is the first model which include both macro and microcirculation information and general subject's characteristics in response to external compression effects. This model can play an important part on future decision making for clinicians in wound healing.

6.2 Limitations of the study and areas for future research

The aim of this thesis was to model the vascular haemodynamics and the distal microcirculation in response to external uniform compression applied to lower limb in humans. The major results and achievements of this research are summarised in the previous section. These results should be viewed as a step towards a better understanding of the mechanism of externally applied pressure on wound healings. Some limitations of our research are outlined below, which will give rise to future work.

- In this research, the experiments and the modelling procedure were independently conducted which has possibly limited the quality of the final modelling expression. Current supervisors were designated after the design and conduct of all the experiments. If both

experimental and mathematical processes could have been closely discussed from the outset, it could have better assisted model design. For instance, the existence of many jumps in measured applied pressure caused many modelling problems. Therefore the pressure could have been applied to the lower limb in a different manner (gradual increase for example). Better models could have been developed using optimally designed experiments.

- The nature of the compression could also be questioned. The external uniform pressure was applied by an inflatable splint. However it is acknowledged that in realistic treatment strategies, the compression is mostly realised by elastic stockings for their ease of use. Similarly, the compression applied to the lower limb was uniform, whereas graduated compression (either from ankle to groin or from ankle to knee) is usually used in hospitals.

- From the experimental point of view, additional data would have been useful for the microcirculation analysis. The pulsed plethysmography of the toe is usually performed in the diagnosis of patient and could have provided further information.

- The modelling approach may also be criticised. The model was built on observed data only and no significant attempt was made to model the physical process.

- Only polynomial forms for the empirical model were used and no other functional forms were considered, on the ground that any function can be approximated by a polynomial.

- The final model was not validated against experiments because there was no test cases. The sample was relatively small to perform a complete analysis. Test cases should have been planned from the outset.

- The volunteers included in the present study were all healthy subjects. Therefore the final model could be implicable to the healthy population. But it cannot be applied to the unhealthy population. Clearly the model will almost always be used in these latter cases.

- The investigation studied the effects of compression in healthy subjects in recumbent position. Other positions should be included as the persons that are treated can also be in standing or semi-recumbent positions.

- At present, there is no applicable software that can be used by clinicians in their daily treatment of wounds. The existence of such software can be of great help.

6.3 Continuing work

Some problems mentioned for future research are to be considered in an extension of the present study at Angers University Hospital:

- Repetition of the experiments on patients with vascular disorders (such as chronic venous insufficiency or occlusive arterial disease)
- Standing subjects to determine the influence of the patient's position on the vascular effects.

In addition it is possible that the following will also be addressed:

- To change the nature of the pressure
- Extension of the model to include additional data

Chapter 7

APPENDIXES

7.1 Appendix A - Protocol description

Effet de la compression sur la circulation des Membres Inférieurs

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Investigateur principal: Professeur J.L. Saumet

Laboratoire d'Explorations Fonctionnelles Vasculaires

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La compression externe des Membres Inférieurs (MI), réalisée le plus souvent par contention élastique, est indiquée pour prévenir ou limiter l'apparition d'oedème. L'étiologie de ces oedèmes est très variée mais on retiendra principalement l'Insuffisance Veineuse Chronique (IVC), l'insuffisance cardiaque, les altérations lymphatiques, etc. Chez les sujets âgés, il n'est pas rare de trouver une association Artériopathie Oblitérante des Membres Inférieurs (AOMI) et IVC et/ou insuffisance cardiaque. De toute façon, les variations tensionnelles et la baisse progressive du débit cardiaque liées au vieillissement sont de nature à changer les effets de la compression externe sur l'hémodynamique des membres inférieurs. Or cette thérapeutique peut avoir des effets néfastes sur le versant artériel et provoquer ou aggraver une ischémie.

Objectif de l'étude

L'objectif principal de cette étude est d'évaluer les effets d'une compression externe d'intensité croissante sur l'hémodynamique artérielle, veineuse et la micro-circulation distale des membres inférieurs.

Méthodologie

Il s'agit d'une étude pilote monocentrique. L'étude débutera dès l'obtention de l'accord du CCPPRB; sa durée sera de 24 mois.

Participants

Le nombre total de sujets est fixé à 80, répartis par groupe afin de permettre une première analyse. Les groupes sont constitués de la manière suivante:

Groupe I	Sujets sains jeunes (18-30 ans)
Groupe II	Sujets sains âgés (50-70 ans)
Groupe III	Patients ayant une AOMI stade II (50-70 ans)
Groupe IV	Patients ayant une IVC (50-70 ans)

Critères de sélection - Inclusion

CRITERES COMMUNS DE SELECTION

Les sujets présentant les caractéristiques suivantes seront sélectionnés pour l'étude:

- Sujets des deux sexes, d'origine caucasienne, et volontaires.
- Aptes à comprendre les objectifs de l'étude et ses contraintes.
- Ayant lu et signé en deux exemplaires le consentement éclairé (un exemplaire lui sera remis après signature de l'investigateur).
- N'ayant pas dépassé le montant annuel autorisé d'indemnité de 25 000 F pour essais thérapeutiques (Loi Huriet 88-1138 du 20/12/88, Arrêté du 21/02/94),
- Affiliés à la sécurité sociale.
- Présentant un électrocardiogramme (ECG) normal, une pression artérielle systolique (PAS) normale comprise entre 100 et 140 mmHg, une pression artérielle diastolique (PAD) normale comprise entre 50 et 95 mmHg (bornes incluses).

CRITERES DE SELECTION DES SUJETS DU GROUPE I

- Agés de 18 à 30 ans.
- Présentant un examen clinique et une exploration fonctionnelle vasculaire normaux.
- Présentant un index de pression (IPSC) systolique à la cheville normal (1<IPSC<1.2), un examen écho Doppler artériel et veineux normal.

CRITERES DE SELECTION DES SUJETS DU GROUPE II

- Agés de 50 à 70 ans.
- Présentant un examen clinique et un examen écho Doppler artériel et veineux normal.
- Présentant un index de pression systolique à la cheville normal (1<IPSC<1.2).

CRITERES DE SELECTION DES SUJETS DU GROUPE III

- Agés de 50 à 70 ans.
- Présentant un index de pression systolique à la cheville inférieur à 0.9.
- Présentant un examen écho Doppler montrant les lésions artérielles.

CRITERES DE SELECTION DES SUJETS DU GROUPE IV

- Agés de 50 à 70 ans.
- Présentant un index de pression systolique à la cheville normal (1<IPSC <1.2).
- Présentant un examen clinique et écho Doppler montrant une insuffisance veineuse chronique mais un état artériel normal pour l'âge du patient.

Critères de non sélection - Non inclusion

Les sujets présentant les critères suivants ne pourront être inclus dans l'étude:

- Age inférieur à 18 ans ou ne correspondant pas à un des quatre groupes.
- N'ayant pas signé le consentement éclairé.
- Difficultés psychologiques ou de compréhension du protocole.
- Pathologie autre que celle prévue dans les groupes patients (groupes III et IV).
- Devant avoir une activité pouvant modifier de façon importante l'état physiologique basal du système vasculaire.

- Ayant une artériopathie des membres inférieurs (indice de pression systolique cheville/bras< 0,9) pour les groupes I, II et IV.
- Présentant un oedème des membres inférieurs pour les groupes I, II et III.
- Présentant un alcoolisme, une toxicomanie ou un tabagisme à plus de 10 cigarettes par jour.
- Pour lesquels une coopération pleine et entière à l'étude est peu probable.

Investigations

BILAN CLINIQUE DE SELECTION - INCLUSION

Il comprendra un interrogatoire du sujet pour connaître ses antécédents médicaux et chirurgicaux.

Un examen clinique approfondi et les examens complémentaires suivants seront réalisés:

- Electrocardiogramme 12 dérivations,
- Mesure de la pression artérielle et de la fréquence cardiaque,
- Echo Doppler des membres inférieurs (artériel et veineux) avec mesure de l'indice de pression systolique cheville/bras,

ETUDE CLINIQUE

Matériel et méthodes

La pression artérielle et la fréquence cardiaque seront mesurées à l'aide d'un appareil semi-automatique par méthode oscillométrique. La pression artérielle moyenne sera calculée par la formule suivante:

$$PAM = PAD + \left[\frac{PAS - PAD}{3}\right]$$

La compression du membre sera réalisée par un pantalon anti-G utilisé par certaines équipes pour limiter une hémorragie interne ou par les laboratoires de recherche en Physiologie aérospatiale.

La circulation dans les artères et les veines du sujet à l'entrée du manchon occlusif sera analysée par Echographie Doppler.

La micro-circulation de l'avant pied par laser Doppler, la pression transcutanée d'oxygène et de dioxyde de carbone seront également mesurés.

Protocole

L'investigation sera réalisée chez les sujets immobiles en décubitus dorsal depuis 20 minutes afin de stabiliser les variables cardio-vasculaires et thermiques.

Un examen allongé sera entrepris après la mise en place des appareils de mesure et des capteurs de compression.

La pression sera augmentée par palier de 10 mmHg jusqu'à l'arrêt circulatoire par gonflage du manchon occlusif. Si le test devient très inconfortable ou douloureux, la pression sera diminuée. Les paramètres seront à nouveau mesurés au cours de décréments de pression de 10 mmHg jusqu'à une pression nulle.

Un test identique sera réalisé en position debout.

Analyse des résultats

La réponse des divers paramètres sera enregistrée et reportée sur des graphiques. Les valeurs moyennes seront comparées et l'analyse permettra de savoir si les différences observées sont significatives. Les résultats seront comparés à une simulation exécutée sur un modèle hémodynamique du membre inférieur.

Cette étude servira de base à une thèse en codirection de l'Université de Glamorgan (Dr R Wiltshire) pour la partie traitement du signal et modélisation et l'Université et le CHU d'Angers (Prof JL Saumet) pour la physiologie circulatoire et la pathologie vasculaire.

Faisabilité

Le service demandeur possède les techniques et le savoir-faire pour la réalisation de l'étude proposée (cf. publication).

Calendrier prévisionnel de l'étude

Date du début de l'étude: JUIN ou JUILLET 1996 selon l'avancement des procédures administratives.

Fin de la phase clinique: JUIN 1998

Considérations éthiques

Généralités

L'étude sera conduite en accord avec les principes énoncés dans la Déclaration d'Helsinki de 1964 révisée à Hong Kong en 1989 et conformément à la loi française sur la protection des personnes se prêtant à une recherche biomédicale.

CCPPRB (Comité Consultatif pour la Protection des Personnes dans la Recherche Biomédicale)

L'investigateur soumettra une copie du protocole ainsi qu'une fiche d'information aux participants au CCPPRB pour avis. L'étude ne débutera qu'après obtention de l'avis favorable du CCPPRB.

Information aux participants

Il est de la responsabilité de l'investigateur d'expliquer au préalable à chaque participant, les objectifs et les contraintes de l'étude. Une copie de la fiche d'information est fournie en annexe 2. Elle sera remise à chaque participant avant le début de l'étude.

Consentement éclairé

Tous les participants doivent donner leur consentement éclairé par écrit, avant d'entrer dans l'étude. Le descriptif du formulaire de consentement, établi en double exemplaire, est donné en annexe 3. Après signature des deux parties, un exemplaire sera remis au participant et un exemplaire sera conservé par l'investigateur.

Note:

Sur la même feuille figurera:

au recto, l'information au patient, au verso, le consentement éclairé.

ANNEXE 1 - BIBLIOGRAPHIE

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ANNEXE 2 - CONSENTEMENT ECLAIRE DU PATIENT

de M..... demeurant:

Effet de la compression sur la circulation des membres inférieurs.

Le Professeur SAUMET et/ou le docteur LEGRAND m'ont proposé de participer à une recherche organisée par l'Unité d'Explorations Vasculaires du CHU d'Angers sur l'effet de la compression sur la circulation des membres inférieurs. Ils m'ont précisé que je suis libre d'accepter ou de refuser de participer à cette étude. J'ai reçu et compris les informations suivantes:

- L'étude va consister à évaluer les effets d'une compression externe d'intensité croissante sur l'hémodynamique artérielle, veineuse et la micro-circulation distale des membres inférieurs.
- Les techniques de mesure ne sont pas vulnérantes (pas de piqûre) et indolores. Une séance de mesure n'exéde pas deux heures et je pourrai l'interrompre à tout moment.

J'autorise les investigateurs à utiliser les résultats de cette étude à des fins scientifiques, mon anonymat étant bien entendu préservé.

J'accepte de participer à cette recherche dans les conditions ci-dessus.

Mon consentement ne décharge pas les organisateurs de la recherche de leurs responsabilités. Je conserve tous mes droits garantis par la loi. Si je désire, je serai libre à tout moment d'arrêter ma participation. J'en informerai alors le Professeur SAUMET ou le docteur LEGRAND. Les données qui me concernent resteront strictement confidentielles. Je n'autorise leur consultation que par des personnes qui collaborent à la recherche désignées par les organisateurs, le Professeur SAUMET ou le docteur LEGRAND et, éventuellement, un représentant des Autorités de Santé. Je pourrai à tout moment demander toute information complémentaire au Professeur SAUMET ou au docteur LEGRAND.

Fait à Angers, le

Signature de l'investigateur

Signature du patient
précédée de la mention "lu et approuvé"

ANNEXE 3 - EFFET DE LA COMPRESSION SUR LA CIRCULATION DES MEMBRES INFERIEURS

INFORMATION AU PATIENT

Il vous est proposé de participer à une étude permettant d'évaluer les effets d'une compression externe croissante sur la circulation artérielle, veineuse, ainsi que la micro-circulation distale des membres inférieurs.

Dans cette étude, plusieurs techniques de mesures seront utilisées:

- Un débitmètre laser Doppler pour mesurer la micro-circulation de l'avant pied. La source lumineuse laser permet d'avoir une lumière très homogène. La puissance de cette source lumineuse laser est quelques dizaines de milliwatts, donc très faible. Cette source laser est très différente de celle utilisée en chirurgie. Cette technique est utilisée depuis plus de 15 ans et à notre connaissance n'a jamais entraîné de lésion cutanée. Votre peau sera donc éclairée par cette lumière laser et la lumière réfléchie par votre peau sera captée et analysée par le débitmètre pour calculer le débit sanguin passant dans vos vaisseaux cutanés.

- Un autre appareil va mesurer la pression de l'oxygène de votre peau. Pour cela, un capteur sera collé à votre peau. Il est thermostaté pour fonctionner à une température bien définie. Cette température est fixée à 44°C. Elle n'entraîne ni douleur ni lésion sur une peau saine.

- La circulation de vos veines et de vos artères sera mesurée par Echographie Doppler.

Les techniques décrites brièvement ci-dessus ne sont ni vulnérantes (pas de piqûre) ni dangereuses et indolores.

Le protocole prévoit qu'une pression sera appliquée sur votre membre inférieur, par paliers, avec un manchon occlusif comme lorsque l'on mesure votre pression artérielle. Mais, dans cette étude, le manchon couvrira tout le membre.

Nous souhaitons pouvoir recueillir les données de votre examen clinique. Aucun examen supplémentaire ne sera réalisé pour les besoins de l'étude.

Votre participation à cette étude est volontaire, si vous souhaitez interrompre votre participation à l'étude vous pouvez le faire à tout moment en prévenant simplement l'un des médecins responsables de l'étude, le Professeur SAUMET et/ou le docteur LEGRAND ou un de leurs collaborateurs médicaux.

Les résultats de cette étude pourront être publiés dans une revue médicale, ou présentés aux autorités administratives. En aucun cas vous ne serez identifié nominativement.

Le CCPPRB d'Angers (Comité Consultatif pour la Protection des Personnes dans la Recherche Biomédicale) a émis un avis favorable le 18 Juin 1996 pour la réalisation de l'étude qui vous est proposée, qu'il l'a jugée conforme aux bonnes pratiques cliniques et respectant la loi relative à la protection des personnes qui se prêtent à une recherche biomédicale.

7.2 Appendix B - Code de la santé publique

CODE DE LA SANTE PUBLIQUE

LIVRE II BIS

PROTECTION DES PERSONNES QUI SE PRETENT A DES RECHERCHES BIOMEDICALES

LOI N°88-1138 du 20 Décembre 1988

Modifiée par

- Loi n°90-86 du 23 janvier 1990
- Loi n°90-545 du 2 juillet 1990
- Loi n°94-630 du 25 juillet 1994 (J.O. du 26 juillet 1994)

L'ASSEMBLEE NATIONALE ET LE SENAT ONT ADOPTE

LE PRESIDENT DE LA REPUBLIQUE PROMULGUE LA LOI DONT LA TENEUR SUIT:

ARTICLE 1er

Il est inséré, après le libre II du Code de la Santé Publique relatif à la protection sanitaire de la famille et de l'enfance, un livre II bis ainsi rédigé:

LIVRE II bis

Protection des personnes qui se prêtent à des recherches biomédicales

ARTICLE L.209-1

(modifié et complété par les articles 35, 36 et 37 de la Loi n° 90.86 du 23 janvier 1990)

Les essais ou expérimentations organisés et pratiqués sur l'être humain en vue du développement des connaissances biologiques ou médicales sont autorisés dans les conditions prévues au présent livre et sont désignés ci-après par les termes: « recherche biomédicale ».

Les recherches biomédicales dont on attend un bénéfice thérapeutique direct pour la personne qui s'y prête sont dénommées recherches biomédicales avec bénéfice individuel direct.

Toutes les autres recherches, quelles portent sur des personnes malades ou non, sont dénommées sans bénéfices individuel direct.

La personne physique ou morale qui prend l'initiative d'une recherche biomédicale sur l'être humain est dénommée ci-après le promoteur. La ou les personnes physiques qui dirigent et surveillent la réalisation de la recherche sont dénommées ci-après les investigateurs.

Lorsque plusieurs personnes prennent l'initiative d'une même recherche, elles peuvent désigner une personne physique ou morale qui aura la qualité de promoteur et assumera les obligations correspondantes en application du présent livre.

Lorsque le promoteur d'une recherche confie sa réalisation à plusieurs investigateurs, il désigne parmi eux un investigateur coordinateur.

TITRE ler

Dispositions générales

ARTICLE L.209-2

Aucune recherche biomédicale ne peut-être effectuée sur l'être humain:

- si elle ne se fonde pas sur le dernier état des connaissances scientifiques et sur une expérimentation préclinique suffisante;
- si le risque prévisible encouru par les personnes qui se prêtent à la recherche est hors de proportion avec le bénéfice escompté pour ces personnes ou l'intérêt de cette recherche;
- si elle ne vise pas à étendre la connaissance scientifique de l'être humain et les moyens susceptibles d'améliorer sa condition.

ARTICLE L.209-3

(complété par l'article 1 de la loi n° 94-630 du 25 juillet 1994)

Les recherches biomédicales ne peuvent être effectuées que:

- sous la direction et sous la surveillance d'un médecin justifiant d'une expérience appropriée;

- dans des conditions matérielles et techniques adaptées à l'essai et compatibles avec les impératif de rigueur scientifique et de sécurité des personnes qui se prêtent à ces recherches. Les recherches biomédicales concernant le domaine de l'odontologie; ne peuvent être effectuées que sous la direction et la surveillance d'un chirurgien dentiste et d'un médecin justifiant d'une expérience appropriée.

Dans les sciences du comportement humain, une personne qualifiée, conjointement avec l'investigateur, peut exercer la direction de la recherche.

ARTICLE L.209-4

(remplacé par l'article 2 de la loi n° 94-630 du 25 juillet 1994)

Les recherches sans bénéfice individuel direct sur les femmes enceintes, les parturientes et les mères qui allaitent ne sont admises que si elle ne présentent aucun risque sérieux prévisible pour leur santé ou celle de leur enfant, si elles sont utiles à la connaissance des phénomènes de la grossesse, de l'accouchement ou de l'allaitement et si elles ne peuvent être réalisées autrement.

ARTICLE L.209-5

(remplacé par l'article 3 de la loi n° 94-630 du 25 juillet 1994)

Les personnes privées de liberté par une décision judiciaire ou administrative, les malades en situation d'urgence et les personnes hospitalisées sans consentement en vertu des articles L.333 et L.342 qui ne sont pas protégées par la loi ne peuvent être sollicités pour se prêter à des recherches biomédicales que s'il en est attendu un bénéfice direct et majeur pour leur santé.

ARTICLE L.209-6

(modifié par l'article 4 de la loi n° 94-630 du 25 juillet 1994)

Les mineurs, les majeurs protégés par la loi et les personnes admises dans un établissement sanitaire ou social à d'autres fins que celle de la recherche ne peuvent être sollicités pour une recherche biomédicale que si l'on peut en attendre un bénéfice direct pour leur santé.

Toutefois, les recherches sans bénéfice individuel direct sont admises si les trois conditions suivantes sont remplies:

- ne présenter aucun risque sérieux prévisible pour leur santé;
- être utiles à des personnes présentant les mêmes caractéristiques d'âge, de maladie ou de handicap;
- ne pouvoir être réalisées autrement.

ARTICLE L.209-7

(modifié par l'article 38 de la loi n° 90-86 du 23 janvier 1990)

(modifié par l'article 5,I et II de a loi 90-630 du 25 juillet 1994)

Pour les recherches biomédicales sans bénéfice individuel direct, le promoteur assume, même sans faute, l'indemnisation des conséquences dommageables de la recherche pour la personne qui s'y prête et celle de ces ayants droits sans que puisse être opposé le fait d'un tiers ou le retrait volontaire de la personne qui avait initialement consenti à se prêter à la recherche.

Pour les recherches biomédicales avec bénéfice individuel direct, le promoteur assume l'indemnisation des conséquences dommageables de la recherche pour la personne qui s'y prête et celle de ses ayants droits, sauf preuve à sa charge que le dommage n'est pas imputable à sa faute ou à celle de tout intervenant, sans que puisse être opposé le fait d'un tiers ou le retrait volontaire de la personne qui avait initialement consenti à se prêter à la recherche.

La recherche biomédicale exige la souscription préalable, par son promoteur d'une assurance garantissant sa responsabilité civile telle qu'elle résulte du présent article et celle de tout intervenant, indépendamment de la nature des liens existant entre les intervenants et le promoteur. Les dispositions du présent article sont d'ordre public.

ARTICLE L.209-8

(modifié par l'article 39 de la loi n° 90-86 du 23 janvier 1990)

La recherche biomédicale ne donne lieu à aucune contrepartie financière directe ou indirecte pour les personnes qui s'y prêtent, hormis le remboursement des frais exposés et sous réserve de dispositions particulières prévues par l'article L 209-15 du présent code relatif aux recherches sans bénéfice individuel direct.

TITRE II

Du consentement

ARTICLE L.209-9

(modifié par l'article 40 de la Loi n° 90.86 du 23 janvier 1990)

(modifié par l'article 6 I - II - III de la loi n° 94-630 du 25 juillet 1994)

Préalablement à la réalisation dune recherche biomédicale sur une personne, le consentement libre, éclairé et exprès de celle-ci doit être recueilli après que l'investigateur, ou un médecin qui le représente, lui a fait connaître:

- l'objectif de la recherche, sa méthodologie et sa durée;
- les bénéfices attendus, les contraintes et les risques prévisibles, y compris en cas d'arrêt de la recherche avant son terme;
- l'avis du comité mentionné à l'article L.209-12 du présent code.
- Le cas échéant, son inscription dans le fichier national prévu à l'article L.209-17.

Il informe la personne dont le consentement est sollicité de son droit de refuser de participer à une recherche ou de retirer son consentement à tout moment sans encourir aucune responsabilité.

L'objectif d'une recherche en psychologie, ainsi que sa méthodologie et sa durée, peuvent ne faire l'objet que d'une information préalable succincte dès lors que la recherche ne porte que sur des volontaires sains et ne présente aucun risque sérieux prévisible. Une information complète sur cette recherche est fournie à l'issue de celle-ci aux personnes s'y étant prêtées. Le projet visé au premier alinéa de l'article L. 209-12 mentionne la nature des informations préalables transmises aux personnes se prêtant à la recherche.

A titre exceptionnel, lorsque dans l'intérêt d'une personne malade, le diagnostic de sa maladie n'a pu lui être révélé, L'investigateur peut, dans le respect de sa confiance, réserver certaines informations liées à ce diagnostic. Dans ce cas, le protocole de la recherche doit mentionner cette éventualité.

Les informations communiquées sont résumées dans un document écrit remis à la personne dont le consentement est sollicité.

Le consentement est donné par écrit ou, en cas d'impossibilité, attesté par un tiers. Ce dernier doit être totalement indépendant de l'investigateur et du promoteur.

Toutefois, en cas de recherches biomédicales à mettre en oeuvre dans des situations d'urgence qui ne permettent pas de recueillir le consentement préalable de la personne qui y sera soumise, le protocole présenté à l'avis du comité instauré par l'article L 209-11 du présent code peut prévoir que le consentement de cette personne ne sera pas recherché et que seul sera sollicité celui des membres de sa famille s'ils sont présents, dans les conditions prévues ci-dessus. L'intéressé sera informé dès que possible et son consentement lui sera demandé pour la poursuite éventuelle de cette recherche.

ARTICLE L.209-10

(modifié par l'article 7 I - II - IV de la loi 94-630 du 25 juillet 1994)

Lorsqu'une recherche biomédicale est effectuée sur les mineurs ou des majeurs protégés par la loi:

- le consentement doit être donné, selon les règles prévues à l'article L 209-9 du présent code, par les titulaires de l'exercice de l'autorité parentale pour les mineurs non émancipés, Pour les mineurs ou les majeurs protégés par la loi, le consentement est donné par le représentant légal pour les recherches avec bénéfice individuel direct ne présentant pas un risque prévisible sérieux et, dans les autres cas, par le représentant légal autorisé par le conseil de famille ou le juge des tutelles;

- le consentement du mineur ou du majeur protégé par la loi doit également être recherché lorsqu'il est apte à exprimer sa volonté. Il ne peut être passé outre à son refus ou à la révocation de son consentement.

TITRE III

Dispositions administratives

ARTICLE L.209-11

(modifié et complété par les articles 41, 42 et 48
de la loi n° 90.86 du 23 janvier 1990)
(modifié par l'article 8 I - II - III - IV - V - VI de la loi n° 94 -630 du 25 juillet 1994)

Dans chaque région, le ministre chargé de la santé agrée un ou, selon les besoins, plusieurs comités consultatifs de protection des personnes dans la recherche biomédicale.

Le ministre fixe par arrêté le nombre de comités dans chaque région. Le champ de compétence territorial d'un comité peut être étendu à plusieurs régions.

Les comités exercent leur mission en toute indépendance. Ils sont dotés de la personnalité juridique.

Les comités sont compétents au sein de la région où ils ont leur siège. Un décret en Conseil d'Etat fixe les conditions minimales d'activité en deçà desquelles le champ de compétence territorial d'un comité peut être étendu à plusieurs régions.

Les comités sont composés de manière à garantir leur indépendance et la diversité des compétences dans le domaine biomédical et à l'égard des questions éthiques, sociales, psychologiques et juridiques.

Leurs membres sont nommés par le représentant de l'Etat dans la région ou le comité a son siège. Ils sont choisis parmi les personnes figurant sur une liste établie sur proposition d'organismes ou d'autorités habilités à le faire, dans des conditions déterminées par décret.

Les membres des comités, les personnes appelées à collaborer à leurs travaux, les agents de l'Etat et les agents relevant de la loi n° 86 - 33 du 9 janvier 1986 portant disposition statutaire relatives à la fonction publique hospitalière qui en sont dépositaires sont tenus, dans les conditions et sous les peines prévues de l'article 378 du Code Pénal, de garder secrètes les informations dont ils peuvent avoir connaissance à raison de leurs fonctions et qui sont relatives à la nature des recherches, aux personnes qui les organisent ou qui s'y prêtent ou aux produits, objets ou méthodes expérimentés.

Ne peuvent valablement participer à une délibération les personnes qui ne sont pas indépendantes du promoteur et de l'investigateur de la recherche examinée.

Les frais de fonctionnement des comités sont financés par le produit d'un doit fixe versé par les promoteurs pour chacun des projets de recherches biomédicales faisant l'objet d'une demande d'avis. Le montant de ce droit est arrêté par le ministre chargé de la santé.

Le ministre chargé de la santé peut retirer l'agrément d'un comité si les conditions d'indépendance, de composition ou de fonctionnement nécessaires pour assurer sa mission dans les meilleures conditions ne sont plus satisfaisantes.

ARTICLE L.209-12

(complété par l'article 43 de la loi n° 90.86 du 23 janvier 1990)

(modifié par l'article 9 I - II - III - IV - V - VI - VII de la loi n° 94-630 du 25 juillet 1994)

Avant de réaliser une recherche biomédicale sur l'être humain, tout investigateur est tenu d'en soumettre le projet à l'avis de l'un des comités consultatifs de protection des personnes dans la recherche biomédicale compétents pour la région où l'investigateur exerce son activité. Il ne peut solliciter qu'un seul avis par projet de recherche.

Dans le cas dune recherche confiée à plusieurs investigateurs, cet avis est demandé par l'investigateur coordonnateur, qui soumet le projet dans les conditions définies au premier alinéa du présent article.

Le comité rend son avis sur les conditions de validité de la recherche au regard de la protection des personnes, notamment la protection des participants, leur information avant et pendant la durée de la recherche et les modalités de recueil de leur consentement, les indemnités éventuellement dues, la pertinence générale du projet et l'adéquation entre les objectifs poursuivis et les moyens mis en oeuvre ainsi que la qualification du ou des investigateurs. Il communique à l'autorité administrative compétente tout avis défavorable donné à un projet de recherche

Avant sa mise en oeuvre, le promoteur transmet à l'autorité administrative Compétente une lettre d'intention décrivant les données essentielles de la recherche, accompagnée de l'avis du comité consulté dans un délai de 5 semaines Il fait connaître par écrit son avis à l'investigateur Cet avis ne le dégage pas de sa responsabilité. Les projets ayant fait l'objet d'un avis défavorable ne peuvent être mis en oeuvre avant un délai de deux mois à compter de leur réception par l'autorité administrative compétente.

Lorsque la recherche doit se dérouler dans un ou plusieurs établissements publics ou privés, le promoteur en informe le ou les directeurs de ces établissements avant que cette recherche ne soit mise en oeuvre.

Le promoteur informe, dès qu'il en a connaissance, l'autorité administrative compétente de tout effet ayant pu contribuer à la survenue d'un décès, provoquer une hospitalisation ou entraîner des séquelles organiques ou fonctionnelles durables et susceptible d'être dû à la recherche. Le promoteur transmet également à l'autorité administrative compétente toute information relative à un fait nouveau concernant le déroulement de la recherche ou le développement du produit ou du dispositif faisant l'objet de la recherche lorsque ce fait nouveau est susceptible de porter atteinte à la sécurité des personnes qui se prêtent à la recherche. Il l'informe enfin de tout arrêt prématuré de la recherche en indiquant le motif de cet arrêt.

L'autorité administrative compétente peut, à tout moment, demander au promoteur des informations complémentaires sur la recherche. En cas d'absence de réponse du promoteur, de risque pour la santé publique ou de non-respect des dispositions du présent livre, elle peut également à tout moment suspendre ou interdire une recherche biomédicale.

ARTICLE L.209-12-1

(ajouté par l'article 10 de la loi n°94-630 du 25 juillet 1994)

Le comité consultatif de protection des personnes peut émettre dans les conditions prévues à l'article L 209-12 un avis favorable à la réalisation d'une recherche sous réserve de la transmission d'informations complémentaires par l'investigateur pendant le déroulement de celle-ci.

A la suite de cette transmission, le comité peut maintenir ou modifier son avis. Cette décision est transmise par écrit à l'investigateur dans un délai de cinq semaines; elle est adressée par le promoteur à l'autorité administrative compétente dans un délai d'une semaine après sa réception.

ARTICLE L.209-13

Les médecins inspecteurs de la santé et les pharmaciens inspecteurs de la santé ont qualité pour veiller au respect des dispositions du présent livre et des textes réglementaires pris pour son application.

ARTICLE L.209-13-1

(ajouté par l'article 15 de la loi n° 94 - 630 du 25 juillet 1994)

Les modalités de consultation des comités consultatifs de protection des personnes dans la recherche biomédicale en ce qui concerne les recherches à caractère militaire sont fixées par décret en Conseil d'Etat.

TITRE IV

Dispositions particulières aux recherches

sans bénéfice individuel direct

ARTICLE L.209-14

(modifié par l'article 11 de la loi n° 94 - 630 du 25 juillet 1994)

Les recherches biomédicales sans bénéfice individuel direct ne doivent comporter aucun risque prévisible sérieux pour la santé des personnes qui s'y prêtent.

Elles doivent être précédées d'un examen médical des personnes concernées. Les résultats de cet examen leur sont communiqués préalablement à l'expression de leur consentement par l'intermédiaire du médecin de leur choix.

ARTICLE L.209-15

(modifié par l'article 12 - I et 11 de la loi n° 94 - 630 du 25 juillet 1994)

Dans le cas d'une recherche sans bénéfice individuel direct à l'égard des personnes qui s'y prêtent, le promoteur peut verser à ces personnes, une indemnité en compensation des contraintes subies. Le montant total des indemnités qu'une personne peut percevoir au cours d'une même année est limité à un maximum fixé par le ministre chargé de la santé.

Les recherches effectuées sur des mineurs, des majeurs protégés par la loi ou des personnes admises dans un établissement sanitaire ou social à d'autres fins que celle de la recherche ne peuvent en aucun cas donner lieu au versement de l'indemnité prévue au premier alinéa du présent article.

ARTICLE L.209-16

(complété par l'article 44 de la loi n° 90 - 86 du 23 janvier 1990)

Toute recherche biomédicale sans bénéfice individuel direct sur une personne qui n'est pas affiliée à un régime de sécurité sociale ou bénéficiaire d'un tel régime est interdite.

L'organisme de sécurité sociale dispose contre le promoteur d'une action en paiement des prestations versées ou fournies.

ARTICLE L.209-17

Nul ne peut se prêter simultanément à plusieurs recherches biomédicales sans bénéfice individuel direct.

Pour chaque recherche sans bénéfice individuel direct, le protocole soumis à l'avis consultatif du comité consultatif de protection des personnes dans la recherche biomédicale détermine une période d'exclusion au cours de laquelle la personne qui s'y prête ne peut participer à une autre recherche sans bénéfice individuel direct. La durée de cette période varie en fonction de la nature de la recherche.

En vue de l'application des dispositions ci-dessus, le ministre chargé de la santé établit et gère un fichier national.

ARTICLE L.209-18

Les recherches biomédicales sans bénéfice individuel direct ne peuvent être réalisées que dans un lieu équipé des moyens matériels et techniques adaptés à la recherche et compatibles avec les impératifs de sécurité des personnes qui s'y prêtent, autorisé, à ce titre, par le ministre chargé de la santé.

ARTICLE L.209-18-1

(ajouté par l'article 19 de la loi n°94-630 du 25 juillet 1994)

Aucune recherche biomédicale ne peut être effectuée sur une personne en état de mort cérébrale sans son consentement exprimé directement ou par le témoignage de sa famille.

Les dispositions de l'article 225-17 du Code Pénal ne sont pas applicables à ces recherches.

TITRE V

Sanctions pénales

ARTICLE L.209-19 (1)

(1) Article en vigueur au 1er mars 1994

Ainsi qu'il est dit à l'article 223-8 du Code Pénal, le fait de pratiquer ou de faire pratiquer sur une personne une recherche biomédicale sans avoir recueilli le consentement libre, éclairé et exprès de l'intéressé, des titulaires de l'autorité parentale ou du tuteur dans les cas prévus par les dispositions du présent code est puni de trois ans d'emprisonnement et de 300.000 francs d'amende.

Les mêmes peines sont applicables lorsque le consentement a été retiré avant qu'il ne soit procédé à la recherche biomédicale.

Ainsi qu'il est dit à l'article 223-9 du Code Pénal, les personnes morales peuvent être déclarées responsables pénalement, dans les conditions prévues par l'article 121-2 du Code Pénal, de cette infraction.

Les peines encourues par les personnes morales sont:

1. L'amende, suivant les modalités prévues par l'article 131-38 du code pénal,
2. Les peines mentionnées à l'article 131-39 du Code Pénal.

L'interdiction mentionnée au 2° de larticle 131-39 du Code Pénal porte sur l'activité dans l'exercice de laquelle ou à l'occasion de laquelle l'infraction a été commise.

ARTICLE L.209-19-1 (1)

Le fait de pratiquer ou de faire pratiquer une recherche biomédicale en infraction aux dispositions des articles L 209-4 à L 209-6 et du dernier alinéa de l'article 209-9 est puni de trois ans d'emprisonnement et de 300.000 francs d'amende.

Les personnes physiques coupables de l'infraction prévue à l'alinéa précédent encourent également les peines suivantes:

1. L'interdiction des droits civiques, civils et de famille, suivant les modalités prévues par l'article 131-26 du Code Pénal;

2. L'interdiction, pour une durée de cinq ans au plus, d'exercer l'activité professionnelle ou sociale à l'occasion de laquelle ou dans l'exercice de laquelle l'infraction a été commise;

3. La confiscation définie à l'article 131-21 du Code Pénal;

4. L'exclusion des marchés publics à titre définitif ou pour une durée de cinq ans au plus.

Les personnes morales peuvent être déclarées responsables pénalement, dans les conditions prévues par l'article 121-2 du Code Pénal, de l'infraction définie à l'alinéa premier.

Les peines encourues par les personnes morales sont:

1. L'amende, suivant les modalité prévues par l'article 131-38 du Code Pénal;

2. Les peines mentionnées à l'article 131-39 du Code Pénal.

L'interdiction mentionnée au 2° de l'article 131-39 du Code Pénal porte sur l'activité dans l'exercice de laquelle ou à l'occasion de laquelle l'infraction a été commise

ARTICLE L.209-20

(modifié par l'article 13 de la loi n° 94-630 du 25 juillet 1994)

Est puni d'un an d'emprisonnement et de 100 000 F d'amende:

- quiconque aura pratiqué ou fait pratiquer une recherche biomédicale sans avoir obtenu l'avis préalable prévu par l'article L 209-12 du présent code;

- quiconque aura pratiqué ou fait pratiquer une recherche biomédicale dans les conditions contraires aux dispositions des deux premiers alinéas de l'article L 209-17 du présent code,

- quiconque aura pratiqué ou fait pratiquer, continué de pratiquer ou de faire pratiquer une recherche biomédicale dont la réalisation a été interdite ou suspendue par le ministre chargé de la santé.

L'investigateur qui réalise une telle recherche en infraction aux dispositions de l'article L 209-18 est puni des mêmes peines.

ARTICLE L.209-21

(complété par l'article 45 de la loi n° 90.86 du 23 janvier 1990)

(modifié par l'article 14 de la loi n° 94 - 630 du 25 juillet 1994)

Le promoteur dont la responsabilité civile n'est pas garantie par l'assurance prévue à l'article L 209-7 du présent code est puni d'un an d'emprisonnement et de 100 000 F d'amende.

Le promoteur qui réalise ou fait réaliser une recherche biomédicale sans avoir transmis au ministre chargé de la santé la lettre d'intention prévue à l'article L209-12 est puni de mêmes peines.

TITRE VI

(ajouté par l'article 46 de la loi n° 90-86 du 23 janvier 1990)

Dispositions diverses

ARTICLE L.209-22

Par dérogation à l'article 13 de la loi des 16 et 24 août 1790 sur l'organisation judiciaire, le Tribunal de Grande Instance est seul compétent pour statuer sur toute action en indemnisation des dommages résultant d'une recherche biomédicale; cette action se prescrit dans les conditions prévues à l'article L 2270-1 du Code Civil.

ARTICLE L.209-23

Les dispositions du présent livre sont applicables dans les collectivités territoriales de Saint-Pierre-et-Miquelon et de Mayotte.

7.3 Appendix C - Cahier d'observation

EFFET DE LA COMPRESSION SUR LA CIRCULATION DES MEMBRES INFERIEURS

Etude pilote monocentrique, contrôlée par:

Professeur Jean-Louis SAUMET

CAHIER D'OBSERVATION

Numéro du sujet ___/___/___

NOM (3 premières lettres) ___/___/___

Prénom (3 premières lettres) ___/___/___

CONFIDENTIEL

IDENTIFICATION DES PERSONNES IMPLIQUEES DANS LE REMPLISSAGE DE CE CAHIER D'OBSERVATION

INVESTIGATEUR PRINCIPAL

Nom: SAUMET **Prénom**: Jean-Louis

Titre: Professeur en Médecine

Adresse professionnelle:

Laboratoire d'Explorations Vasculaires - CHRU d'ANGERS - 49033 ANGERS Cedex

Tél.: 02 41 35 36 89

CO-INVESTIGATEUR

Nom: LEGRAND **Prénom**: Marie-Sophie

Titre: Docteur en Médecine

Adresse professionnelle:

Laboratoire d'Explorations Vasculaires - CHRU d'ANGERS - 49033 ANGERS Cedex

Tél: 02 41 35 36 67

ATTESTATION D'OBTENTION DU CONSENTEMENT ECLAIRE

Je soussigné(e) Docteur.....atteste avoir obtenu le consentement libre et éclairé du participant à l'étude après l'avoir informé des points suivants:

- l'objectif de la recherche, sa méthodologie, sa durée,
- les risques et contraintes prévisibles,
- l'avis du CCPPRB,
- son droit de refuser de participer à une recherche ou de retirer son consentement à tout moment sans encourir aucune responsabilité.

L'accord du *participant* a été obtenu par écrit.

Date de l'obtention du consentement éclairé: ___/___/___

Signature de l'investigateur:

VISITE DE SELECTION

- Critères de sélection
- Démographie
- Activité professionnelle
- Biométrie
- Facteurs de risque
- Examen clinique
- Examen cardiovasculaire
- Echo doppler
- Statut du sujet

Date: ___/___/___

Critères de sélection:

OUI

Sujet volontaire, caucasien.....

Agé de 18 à 30 ans ou de 50 à 70 ans.....

Apte à comprendre les objectifs de l'étude.....

Ayant lu et signé le consentement éclairé.....

Sujet n'ayant pas dépassé le montant annuel autorisé d'indemnités de 25 000Frs.....

Sujet affilié à la sécurité sociale.....

NON

Sujet participant à une autre étude de manière contemporaine ou ayant participé.....

à une étude au cours du mois précédent

Sujet devant avoir une activité pouvant modifier de façon importante .....

l'état physiologique basal du système vasculaire

Sujet présentant un oedème des membres inférieurs.....

Antécédents d'alcoolisme, de toxicomanie ou de tabagisme (>10 cigarettes/jour) .....

Coopération pleine et entière peu probable.....

Démographie:

Nom: _____

Prénom: _____

Date de naissance: ___/___/___

Age: _____ans

Sexe: _____

Race: Caucasien

Activité professionnelle:

Activité: ___

0 = Sans

1 = En formation

2 = Travail à temps partiel

3 = Travail à temps plein

4 = Chômage

5 = Retraité

6 = Autre, préciser .....

Type d'activité: ___

1 = Ouvrier

2 = Employé

3 = Artisan / commerçant

4 = Fonctionnaire

5 = Cadre / Prof. libérale

6 = Etudiant

7 = Autre, préciser .....

Affilié à la sécurité sociale: oui / non*

n°: _____

* Si non, le sujet ne peut être sélectionné dans l'étude.

Biométrie:

Poids: _____kg

Taille: _____cm

Facteurs de risque:

Tabagisme:

0: Nul

1: Ancien. Nombre de paquet/jour = ____ pdant _____ans, soit _____ paquet/année

Date de l'arrêt: ___/___/___

2: Actuel Nombre de paquet/jour = ____ depuis _____ans, soit _____ paquet/année

Demander aux fumeurs de ne pas fumer de cigarette dans les 12 heures qui précèderont l'expérience.

Alcoolisme:

0: Nul

1: Ancien. Nombre de litre d'alcool/jour = _____ pdant _____ans

Date de larrêt: ___/___/___

2: Actuel Nombre de litre d'alcool/jour = _____ pdant _____ans

Examen clinique:_____

_____ _____

_____

_____

_____

Examen cardiovasculaire:

Mesures des pressions artérielles:

Pressions artérielles humérales en décubitus:

Droite

PAS = _____mmHg

PAD = _____mmHg

PAM = _____mmHg

Gauche

PAS = _____mmHg

PAD = _____mmHg

PAM = _____mmHg

Pressions artérielles tibiales en décubitus:

Droite

PAS = _____mmHg

PAD = _____mmHg

PAM = _____mmHg

Gauche

PAS = _____mmHg

PAD = _____mmHg

PAM = _____mmHg

Index de pression systolique à la cheville, au repos:

A droite _____

A gauche _____

normal: 1<IPSC<1.2 / AOMI: IPSC<0.9

ECG:

Normal / Anormal

Commentaires: _____

_____

_____

_____

_____

Echo doppler:

Système veineux:

Normal / Anormal

Commentaires: _____

_____

_____

_____

_____

Système artériel:

Normal / Anormal

Commentaires: _____

_____

_____

_____

_____

Statut du sujet:

Le sujet est sélectionné dans le groupe d'étude n°: _____

I Sain jeune (18-30 ans)

II Sain âgé (50-70 ans)

III AOMI stade II (50-70 ans)

IV IVC (50-70 ans)

0 Le sujet n'est pas sélectionné dans l'étude.

Date de la prochaine visite: ___/___/___

7.4 Appendix D - Fiche de renseignements

FICHE DE RENSEIGNEMENTS

Nom et prénom du sujet: .....

Catégorie du sujet: .....

Date de naissance: ..... Age: .....ans

Taille: .....m Circonférence mi-mollet = ...cm

Poids: .....kg Circonférence mi-cuisse = ...cm

Fumeur: OUI / NON

Combien ? .....

Electrocardiogramme normal ? .....

IPSC = ... (normal: 1<IPSC<1.2 / AOMI: IPSC<0.9)

Date de la manip: .....

Heure en début de manip: .....(montre), ...(Acuson), ...(Dinamap)

Salle de manip: ..n°.....

Température: .....°C Hygrométrie: .....%

Manchon sur jambe: droite / gauche

Brassard Dinamap sur bras: droit / gauche

Laser voie 1 sur pied: droit / gauche

Température voie 1 sur pied: droit / gauche

TcPO2-1 (voies 5&7) sur pied: droit / gauche

Annotations complémentaires:

.....Nom de sauvegarde du fichier .....

.....Enregistrement vidéo sur cassette n°.....

.....

7.5 Appendix E - Article accepted in *Cardiovascular Research*

Effects of positive pressure on both femoral venous and arterial blood velocities and the cutaneous microcirculation of the forefoot

Bérengère Fromy, BSc; Marie-Sophie Legrand, MD; Pierre Abraham, MD, PhD; Georges Leftheriotis, MD, PhD; Paul Cales, MD; Jean-Louis Saumet, MD, PhD

Objective: The balance between the apparent beneficial effect and the risk of arterial ischaemia resulting from an external uniform compression is unclear. The purpose of the study was to determine the effects of a positive uniform compression on the lower limb circulation until a critical threshold was reached.

Methods: We used Doppler ultrasound to measure femoral venous and arterial blood velocities. The effects of positive pressure on cutaneous microcirculation were evaluated by laser Doppler flux (LDF), transcutaneous oxygen pressure (tcpO2) and transcutaneous carbon dioxide pressure (tcpCO2) on the forefoot of 17 healthy subjects.

Results: The results are expressed as median [lowest observed value-highest observed value]. Whereas the arterial femoral velocity (A.F.V.) decreased from 0.21 [0.08-0.36] to 0.17 [0.08-0.28] $m.s^{-1}$ for an external pressure as low as 10 mmHg ($p<0.001$), the venous femoral velocity (V.F.V.) decreased from 0.13 [0.06-0.40] to 0.09 [0.05-0.34] $m.s^{-1}$ at 20 mmHg ($p<0.001$). The increase of tcpCO2 from 39.8 [29.9-53.7] to 40.2 [30.0-55.5] mmHg ($p<0.05$) and the decrease of LDF from 8.7 [3.1-25.9] to 5.5 [2.3-21.1] A.U ($p<0.001$) occurred at 10 mmHg. However tcpO2 decreased only from 76.7 [40.2-91.2] to 64.6 [18.9-85.2] mmHg when the splint pressure reached 60 mmHg ($p<0.05$). The observed parameters (LDF, tcpO2, V.F.V. and A.F.V.) further decreased (except for tcpCO2 which increased) up to the end of the study as the applied pressure was increased.

Conclusion: Positive pressure on the full leg provided no significant beneficial effect on femoral venous blood velocity. Whereas we showed that for an external uniform pressure as low as 10 mmHg, significant impairments in both arterial inflow of the lower limb and microcirculation of the forefoot appeared in recumbent healthy young subjects.

Keywords: positive pressure, laser Doppler, microcirculation, ischaemia, femoral blood velocities

1. Introduction

The external compression on the lower extremities, mostly realised by elastic compression, is used to prevent or to limit the oedema formation of various origin: chronic venous insufficiency, cardiac insufficiency, lymphatic alterations are mainly considered. On the other hand, a direct inverse relationship exists between skin blood flow and local applied pressure [1,2]. Moreover an inverse relationship between transcutaneous oxygen pressure (tcpO2) and external pressure has been found, although controversy exists whether it is linear or parabolic [3,4]. In attempting to find an explanation for the apparent beneficial effect of compression on venous function suggested as resulting from an improvement in calf muscle pump function with an increase in venous flow velocity or a reduction in venous reflux, studies have focused attention on the flow of blood in the deep or superficial venous system of the lower limbs [5,6].

A local external applied pressure as low as 40 mmHg produces a significant decrease upon transcutaneous oxygen tension and even a compression of 20 mmHg can decrease significantly the skin blood flow [2]. As the level of applied pressure in both studies varied in the same range, the balance between the beneficial effect on the venous circulation and the risk of tissue ischaemia due to an external uniform compression is still to be evaluated.

Thereby the purpose of this study was to determine the effects of a positive uniform compression applied to the whole lower limb on both femoral venous and arterial blood velocities and the cutaneous microcirculation of the forefoot until a critical threshold was reached.

2. Methods

2.1 Population

Seventeen healthy Caucasian subjects participated in the present study. The participants included 8 young males with a median age of 24 [23-28] years, weight of 68 [62-82] kg, and height of 175 [169-182] cm and 9 young females with a median age of 23 [20-26] years, weight of 59 [47-73] kg, and height of 165 [160-180] cm. All volunteers gave their written informed consent to participate to the experimental protocol which was approved by our institutional review committee according to the Helsinki Declaration. After a physical examination, a 12-lead electrocardiogram, the measurements of the ankle to brachial systolic pressure ratio in both limbs, veins and arteries of abdominal and lower limbs examination by colour Duplex scanning

were performed in order to exclude subject with significant cardiovascular disease.

2.2 Measured data

Ultrasound imaging of the femoral vessels was performed with a 7 MHz linear electronic transducer (ACUSON 128XP10 - Mountain View - California - USA). Ultrasound coupling between skin and probe was achieved by a large amount of ultrasound transmission gel, avoiding direct contact influence of the probe with the skin. The femoral vessel was scanned in transversal plane and a regular segment of the common femoral vein was pointed with an indelible marker on the skin, very close to the saphenofemoral junction. The probe was then turned 90 degrees to display a longitudinal view of the vessel and to measure both arterial femoral velocity (A.F.V.) and the venous femoral velocity (V.F.V.) distal to the saphenofemoral junction. Using a maximal true angle between the probe and the skin and an inclined Doppler axis of 20°, the complementary angle to align with the vessel axis was inferior to 60° in all cases. Both arterial and venous blood flow velocities were the average of the maximal velocities on a 8 seconds recording as previously reported [7-9] (included eventual arterial diastolic zero flow), and were not angle corrected.

Transcutaneous oxygen pressure (tcpO2), based upon the electrochemical reduction of oxygen, was measured using a Clark-type oxygen sensing electrode [10,11]. Transcutaneous carbon dioxide pressure (tcpCO2) was measured using a Severinghaus-type carbon dioxide electrode. A combined transcutaneous oxygen pressure and carbon dioxide pressure electrode comprising a heating element, two temperature sensors and the gas measurements electrodes in a single unit was used (TCM3 Radiometer - Copenhagen - Denmark) and placed distal to the splint. The electrode was attached to the skin on the forefoot with a double-sided adhesive ring tape, the heat generated, automatically stabilised to 44.5°C, was transferred from the heating element via the silver body to the skin surface. This heating produced local vasodilation, increasing the permeability of the skin to oxygen and carbon dioxide, and allowing measurement on the skin surface. All tcpO2 and tcpCO2 measurements were made with the subjects breathing room air, and the data were expressed in millimetres of mercury and automatically corrected to 37°C.

Cutaneous blood flow of the foot was measured using a laser Doppler flowmeter (Periflux 4001, Perimed AB - Järfälla - Sweden) applied to the skin of the forefoot with a plastic holder. The helium-neon laser Doppler velocimeter uses a monochromatic light source at 780 nm.

Conducted to the body surface via fibber optics, the laser light illuminates and permeates the skin in a diffuse way [12-16]. Doppler-shifted light, proportional to the product of velocity and the concentration of moving red blood cells within the surface capillaries of the skin [14], is processed and expressed in arbitrary units (A.U). Comparison with non invasive techniques such as plethysmography or thermal clearance showed that laser Doppler flux (LDF) provides accurate measurement of skin blood flow in human limb [17,18] and is used widely in the investigation of the skin microcirculation [7,19,20]. We have previously shown that cutaneous LDF is not influenced by underlying tissue blood flow [21].

2.3 Data collection

The resulting analogue output laser Doppler signals, tcpO2 and tcpCO2 signals in both feet and the pressure in the full-leg splint were recorded by means of a data acquisition system (MP100, Biopac System Inc., Santa Barbara, California - USA) and further analysis was performed by a specific software (Acknowledge, Biopac System Inc., Santa Barbara, California - USA). The sampling acquisition was fixed to 25 samples per second.

Lastly heart rate and arm systolic and diastolic blood pressures were recorded during the whole experiment using an automatic 16 cm large cuff inflation system (Dinamap 1846SX/P, Critikon, Johnson & Johnson - Tampa, Fl. USA) in order to check the stability of the general haemodynamic parameters of the participant over the experiment.

2.4 Experimental protocol

A standard inflatable splint extending from the ankle to the upper thigh (Mast III-AT anti shock trousers, David Clark company, Worcester UK) was placed around the right leg. The skin of each subject was cleansed with the use of alcohol tabs at the selected measuring sites. The subject, fully equipped, was placed supine upon an examination table with a pillow under the head, in a quiet room for 20 minutes to allow stable conditions at rest. The room temperature was maintained at 25 [23-27]°C and the hygrometry was 58 [52-68]%. Once the measurements started, each subject was asked to lie immobile until the end of the experiment.

After measurements in the basal conditions were achieved, the splint was inflated to 10 mmHg and maintained for three minutes. During the last two minutes, the sonographic measurements were achieved by a well trained physician. Each step duration was 3 minutes in total. After this first step, the inflation of the splint was increased at 20 mmHg, then successively

increased by step of 20 mmHg. The experiment was ended when no decrease in LDF and tcpO2 was observed between two successive levels of splint pressure. The minimum values were defined as the physiological zero of the participant, observed at the individual maximum reached splint pressure.

2.5 Statistical analysis

The results are expressed as median [lowest observed value-highest observed value]. Analyses of differences between paired values were carried out using the non parametric Wilcoxon matched-pairs signed-ranks test (for within subjects differences) with the basal condition (splint not inflated) as the reference. The p values were calculated considering the number of participants at each pressure. A p value of less than 0.05 was considered significant. Statistical computation was carried out with use of the Statistical Package for Social Sciences (SPSS Inc. Chicago, Ill.).

3. Results

Every subject had stable heart rate and arm systolic and diastolic blood pressures during the full duration of the experiment. These measured parameters did not change significantly: from 62 [45-80] min-1, 108 [90-123] mmHg, 58 [54-74] mmHg to 66 [44-86] min-1, 111 [95-144] mmHg, 63 [50-81] mmHg over the three first minutes and the three last minutes of the experiment respectively. The results of various splint pressures on laser Doppler flow, tcpO2, tcpCO2, venous and arterial femoral velocities are summarised in table I for all subjects (n=17). The minimum values were reached at 80 mmHg in 11 subjects. Therefore only 6 subjects were observed at a pressure of 100 mmHg. The mean pressure in the splint to reach the physiological zero was 80 [80-100] mmHg for the overall of the participants.

Pressure	0	10	20	40	60	80	100
V.F.V.	0.13	0.10	0.09 ***	0.07 ***	0.05 ***	0.04 ***	0.01 *
($m.s^{-1}$)	[0.06-0.40]	[0.05-0.36]	[0.05-0.34]	[0.03-0.18]	[0.01-0.09]	[0.00-0.11]	[0.01-0.04]
A.F.V.	0.21	0.17 ***	0.14 ***	0.11 ***	0.08 ***	0.05 ***	0.04 *
($m.s^{-1}$)	[0.08-0.36]	[0.08-0.28]	[0.05-0.26]	[0.03-0.19]	[0.03-0.13]	[0.01-0.11]	[0.01-0.06]
LDF	8.7	5.5 ***	6.0 ***	5.8 **	4.0 ***	3.1 ***	2.5 *
(A.U)	[3.1-25.9]	[2.3-21.1]	[2.2-18.9]	[1.9-13.9]	[1.8-11.1]	[1.5-11.1]	[1.2-4.1]
tcpO2	76.7	75.2	72.8	75.7	64.6 *	40.9 ***	17.3 *
(mmHg)	[40.2-91.2]	[36.8-90.5]	[33.8-88.1]	[32.6-87.5]	[18.9-85.2]	[4.4-83.4]	[7.3-57.7]
tcpCO2	39.8	40.2 *	41.0 *	41.8 **	42.6 ***	44.4 ***	44.4 *
(mmHg)	[29.9-53.7]	[30.0-55.5]	[30.6-56.5]	[30.7-57.1]	[30.6-58.6]	[33.0-63.6]	[38.3-55.3]
n	17	17	17	17	17	17	6

*, $p<0.05$; **, $p<0.01$; ***, $p<0.001$. The results are expressed as median [lowest observed value-highest observed value].

Table I. Effects of uniform positive compression on both venous and arterial femoral velocities and forefoot cutaneous microcirculation on young healthy subjects

There was no significant change in the V.F.V. at a splint pressure of 10 mmHg. A 20 mmHg compression reduced significantly ($p<0.001$) the venous femoral velocity: an average of 30.8 % decrease compared to basal condition. The venous velocity further decreased as the applied pressure was increased. At the individual maximum splint pressure, the maximal decrease in venous velocity compared to resting value was 84.6 % ($p<0.05$).

The A.F.V. decreased for external pressure as low as 10 mmHg ($p<0.001$). The minimum arterial femoral velocity was 0.04 [0.01-0.11] $m.s^{-1}$ at the individual maximum splint pressure, representing a 81.0 % decrease compared to the basal velocity ($p<0.05$).

Although it trended to decrease, no significant change was found for tcpO2 before the splint pressure reached 60 mmHg. However tcpCO2 values increased significantly ($p<0.05$) at 10 mmHg and further increased up to the end of the study.

A significant decrease in LDF (36.8 % compared to the mean resting value) measured on the forefoot yet occurred when the external pressure was 10 mmHg ($p<0.001$). The LDF continued to decrease until a minimum skin blood flow level of 3.0 [1.2-11.1] A.U (65.5 % decrease compared to the basal condition), although this minimum value was reached at different splint pressures (80 or 100 mmHg) according to each participant.

4. Discussion

The findings of the present investigation demonstrated a significant impairment of A.F.V., LDF and tcpCO2 with compressive value as low as 10 mmHg, although V.F.V. and tcpO2 were not decreased. On the other hand, in our experiment conditions, tcpO2 appears less relevant than LDF and tcpCO2 to evaluate local micro-circulatory impairment.

Very little information is available regarding the effect of external compression on venous blood flow in the total extremities [22,23]. On the other hand, few results are available of the effect of uniform compression on arterial blood flow [24], since most recent studies have been performed on the effects of local applied pressure on the microcirculation [25,26]. Even less is known regarding the effects of externally applied pressure on both venous and arterial blood flow, and distal microcirculation.

The applied pressure produced by elastic compression or bandages can be classified according to the amount of compression [27]. The compression bandages range from 14 to 17 mmHg for the light compression bandages, from 18 to 24 mmHg for moderate compression bandages, from 25 to 35 mmHg for high compression bandages, and is up to 60 mmHg for extra high-performance compression bandages [28]. Nevertheless as already underlined, the pressure values used in the patient management is of the same range than those discriminated for an arterial ischaemia.

Sabri et al. found that a 5 mmHg inflatable splint compression produces a non-significant increase in the femoral arterial and venous flows [29]. Unfortunately, the arterial flow was measured in dogs, whereas the venous flow was measured in humans. They mentioned that a higher compression pressure is required before any significant decrease of the femoral venous blood flow can be seen. Inversely, Spiro et al. mentioned an increase of 13% of the femoral vein flow in both limbs at 5 mmHg by inflatable splint [30], but no statistical analysis was made in this study. However they concluded that the optimum pressure usually lies between 5 and 12

mmHg but may well vary from patient to patient depending on such factors as limb adiposity, limb circumference, the presence of lymphoedema, or previous episodes of thrombosis. Our results are consistent with Sabri et al. investigation, as we showed that there was no significant increase of the femoral venous velocity at a 10 mmHg compression and that the venous velocity decreased significantly at 20 mmHg splint pressure.

Otherwise we found that a significant decrease of 19.0 % compared to resting value in maximal arterial inflow occurred for splint pressure as low as 10 mmHg. In agreement with our investigation, Sabri, et al showed that " a compression pressure exceeding 5 mmHg produces a progressive diminution of the femoral arterial blood flow " [29]. Halperin et al. reported also that an external applied pressure of 10 mmHg was sufficient to reduce the arterial circulation in normal limbs [24]. They attributed the resultant decrease of arterial inflow and venous outflow to two possible factors: first, a reduction of arteriovenous pressure gradients, and, secondly, a decrease in the calibre of small vessels in the compressed area that caused an increase in resistance to flow. Consistently with arterial flow decrease produced by 10 mmHg, the skin blood flow showed a significant decrease at 10 mmHg.

The tcpO2 decrease with increasing pressure shown in recumbent subjects found in the present study is in agreement with Gaylarde et al. who mentioned that a compression of the lower limb whilst the subject is recumbent leads to a fall in tcpO2. This author suggested that when the patient is confined to bed, only lightweight stockings (the applied pressure lies between 5 and 10 mmHg) are safe in the prophylaxis of post-operative deep-vein thrombosis [31]. However our results suggest that tcpO2 alone does not interpret the arterial haemodynamics properly in our experimental conditions. Indeed a significant decrease was observed only at 60 mmHg with tcpO2 readings. Maybe the skin blood flow impairment due to a splint pressure up to 60 mmHg was not important enough. On the other hand; for normal arteriolar pressure values, tcpO2 mainly reflects arterial pO2. TcpO2 becomes flow dependant only when arterial pressure is reduced below a certain threshold [2]. The late decrease of the tcpO2 values found in the present work may result from relative uncompromised distal arteriolar pressures. Since arteriolar pressure in the foot was not recorded in the present study, this hypothesis cannot be proved. Nevertheless for a pressure as low as 10 mmHg, tcpCO2 increased significantly, while LDF decreased significantly. We hypothesise that pH increased and that a distal micro-

circulation impairment was already observed on the forefoot. Andreozzi et al. already showed that a dissociation between tcpO2 and tcpCO2 exists [32]. In a further study, they mentioned that " in some cases, the tcpO2 cannot provide correct assessment of the risk of skin necrosis, while tcpCO2 measurement could " [33]. In the other hand, some authors already mentioned that a significant difference exists between tcpO2 and LDF changes at the forefoot to different physiological stresses [34]. Therefore, tcpO2 measurement on its own may be not a sufficient tool in our experimental conditions to control the distal microcirculation.

From this study it can be seen that positive pressure on the full leg provided no significant beneficial effect on femoral venous blood velocity. Whereas we showed that for an external uniform pressure as low as 10 mmHg, significant impairments in both arterial inflow of the lower limb and microcirculation of the forefoot appeared in recumbent healthy young subjects. Although such a result was found in healthy volunteers, the technique used in the present work is an interesting approach in the understanding of the compression effects. A study of patients with vascular disease, both arterial and venous, would be relevant. It might allow a better understanding of potential beneficial and harmful effects of compression in such patients groups. Further work and additional data will be necessary to sort out these issues.

References

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7.6 Appendix F - Statistical theory

Least squares method

Least squares method can be used to establish the existence of a linear relation between two variables. This is a method that is used to find a straight line that can best approximate for the relationship between the independent and dependent variables. We refer to the equation of the line developed using least squares method as the estimated regression line, or the estimated regression equation defined as follows:

$$\hat{y} = b_0 + b_1 x$$

where

$b_0 = y$−intercept of the line

b_1 = slope of the line

$\hat{y}$ = estimated value of the dependent variable given x

For any particular value, x_i, of the independent variable x, the corresponding value on the estimated regression line is denoted by

$$\hat{y}_i = b_0 + b_1 x_i$$

Application of the least squares method provides the values of b_0 and b_1 that make the sum of the squared deviations between the observed values of the dependent variable y_i and the estimated values of the dependent variable $\hat{y}_i$ a minimum. The criterion for the least squares method is to find b_0 and b_1 so that:

$$\sum (y_i - \hat{y}_i)^2$$

is minimum, where

y_i = the ith observed value of the dependent variable

$\hat{y}_i$ = the ith estimated value of the dependent variable

The resulting estimates for b_0 and b_1 are:

$$b_1 = \frac{\sum_{i=1}^{n} y_i x_i - \frac{\left(\sum_{i=1}^{n} y_i\right)\left(\sum_{i=1}^{n} x_i\right)}{n}}{\sum_{i=1}^{n} x_i^2 - \frac{\left(\sum_{i=1}^{n} x_i\right)^2}{n}}, \quad b_0 = \overline{y} - b_1\overline{x}$$

If some other criterion were used, such as minimising the sum of the absolute deviations between y_i and $\hat{y}_i$, a different equation would be obtained. In practice, the least squares method is the most widely used.

In multiple regression, extensions of the concepts of simple linear regression are used to develop an estimated regression equation for predicting y based on several independent variables. The basic principles are the same as in the case of a single variable, but instead of a regression equation involving a single variable x, we will have a multiple regression equation:

$$\hat{y} = b_0 + b_1 x_1 + b_2 x_2 + ... + b_p x_p$$

where, for example, x_2 can represent x_1^2.

The linear regression procedure in SPSS estimates the coefficients of the linear equation, involving a set of independent variables, that best predicts the value of the dependent variable using one particular method. The available options are Enter, Remove, Stepwise, Backward, and Forward. The package provides extensive diagnostic facilities to help the user to determine how well the model fits.

Indeed the available statistical results in SPSS for the regression coefficients are the estimates which are the coefficients themselves, confidence intervals (95% confidence intervals for the coefficients), and the covariance matrix that gives the variances and covariances among the coefficient estimates. Moreover the descriptive provides the means and standard deviations of each variable in the analysis, plus a correlation matrix (with one-tailed significance level and number of cases for each correlation). Finally, model fit statistics include multiple R, R squared and adjusted R squared, standard error of the estimate, and an analysis-of-variance table.

The coefficient of determination - R Square

The difference between y_i and $\hat{y}_i$represents the error in using $\hat{y}_i$ to estimate y_i ; the difference for the ith observation is $y_i - \hat{y}_i$. This difference is referred to as the ith residual. Thus the sum of squares minimised by the least squares method is referred to as the sum of squares due to error (SSE), or the **residual sum of squares** (as it is denoted in SPSS).

$$SSE = \sum \left(y_i - \hat{y}_i \right)^2$$

The corresponding sum of squares about the mean, denoted by SST (Total Sum of Square), is as follows:

$$SST = \sum \left(y_i - \bar{y} \right)^2$$

where $\bar{y}$ = mean value for the dependent variable.

To measure how much the predicted values $\hat{y}$ on the estimated regression line deviate from $\bar{y}$, another sum of squares is computed. This sum of squares is called the sum of squares due to regression and is denoted by SSR. The sum of squares due to regression can be written as follows:

$$SSR = \sum \left(\hat{y}_i - \bar{y} \right)^2 = SST - SSE$$

The ratio SSR/SST can be used to evaluate the goodness of fit for the regression relationship. This ratio is called the **coefficient of determination** and is denoted r^2, and in general $0 < r^2 < 1$. Larger values of r^2 indicate a better fit. However, the values of r^2 does not allow to conclude whether a regression relationship is statistically significant. To draw conclusions concerning statistical significance, other measures are needed.

In multiple regression analysis, a similar quantity is computed. This is called the multiple coefficient of determination:

$$R^2 = \frac{SSR}{SST}$$

The adjusted multiple coefficient of determination - Adjusted R Square

In general, it is always true that R^2 will increase as more independent variables are added to the regression model because adding variables to the model causes the prediction errors to be smaller, hence reducing SSE. Since $SST = SSR + SSE$, when SSE gets smaller, SSR must get larger, causing R^2 to increase. This is often stated as over-parameterisation and must be exercised with care.

Many analysists recommend adjusting R^2 for the number of independent variables to avoid overestimating the impact of adding an independent variable on the amount of explained variability. This *adjusted multiple coefficient of determination*, denoted **Adjusted R Square** in SPSS, is computed as follows:

$$Adjusted\ R\ Square = 1 - \left(1 - R^2\right) \frac{n-1}{n-p-1}$$

where

n = total number of observations

p = number of independent variables

Degrees of freedom (DF)

The sum of squares due to regression (SSR) has p degrees of freedom corresponding to the p independent variables.

First recall that SSE is a measure of the variability of the actual observations about the estimated regression equation. Every sum of squares has associated with it a number called its degrees of freedom. The degrees of freedom indicates how many independent pieces of information involving the n independent values y_1, y_2, ...y_n are used to compute the sum of squares. Statisticians have shown that SSE has $n - p - 1$ degrees of freedom.

As in the case of estimating p and q so that $p + q = 1$, only one of the unknowns need to be estimated. In the case of p independent variables in a multiple regression, p mean values and a total mean will reduce the degrees of freedom from n to $n - p - 1$.

Mean squared

Mean squared is a number computed by dividing a sum of squares by its degrees of freedom. Thus, the mean square due to error, also referred to as mean squared error, is computed by dividing SSE by its degrees of freedom, $n-p-1$.

$$MSE = \frac{SSE}{n-p-1}$$

Similarly the mean square due to regression is computed as follows:

$$MSR = \frac{SSR}{p}$$

F

The test concerning the significance of the regression relationship is based on the following F statistic:

$$F = \frac{\text{Mean Square Regression}}{\text{Mean Square Error}}$$

This is referred as F with p, $n-p-1$ degrees of freedom. Critical values for F can be found from F-tables for different levels of significance. This is compared to for the observed F value to reject, or not to reject the hypothesis (if $F_{observed} > F_{theory}$).

Multicollinearity

We have used the term *independent variable* in regression analysis to refer to any variable being used to predict or explain the value of the dependent variable. The application of regression requires these explanatory variables to be independent. However, in practice, this condition is hardly achieved. Most explanatory variables used in a multiple regression problem are correlated to some degree with one another. The existence of a 'high' correlation between these variables can create a problem in the parameters estimations of the regression equation.

This problem is referred to as multi-collinearity in regression analysis.

LAG function

In studying the impact of one explanatory variable on some explained variable, it is often the case that movements in the explanatory variable require some time to influence changes in the explained variable. This phenomena is referred to a delay pattern. In technical terms, the regression analysis is performed on the delayed (or lagged) values of the explanatory variable.

The Transform menu in SPSS is used in order to create a time series. The different commands available in this menu are the following: Compute, Random Number Seed, Count, Recode: Into Same Variables, Recode: Into Different Variables, Rank Cases, Automatic Recode, Create Time Series, Replace Missing Values, Run Pending Transforms.

New time series variables can be created as functions of existing series, for example, lagged or leading values, differences, cumulative sums.

In the case of the Lag function, each value is replaced by the value of a preceding case. The order specifies how far distant the preceding case is. For an order of 1, the value of the immediately preceding case is used.

7.7 Appendix G - Catastrophe theory

7.7.1 Introduction

Catastrophe theory is a mathematical language created to describe and classify particular discontonuities. This new mathematical method for describing the evolution of forms in nature was created by René Thom who wrote a revolutionary book « Structural stability and morphogenesis » in 1972 expanding the philosophy behind the ideas. It is particularly applicable where gradually changing forces produce sudden changes in effects. We often call such effects catastrophes, because our intuition about underlying continuity of the forces makes the very discontinuity of the effects so unexpected, and this has given rise to the name. The theory depends upon some new and deep theorems in the geometry of many dimensions, which classify the way that discontinuities can occur in terms of a few archetypal forms; Thom calls these forms the ELEMENTARY CATASTROPHES. The remarkable thing about the results is that, although the proofs are sophisticated, the elementary catastrophes themselves are both surprising and relatively easy to understand, and can be profitably used by scientists who are not expert mathematicians.

7.7.2 The seven elementary catastrophes

The number of qualitatively different configurations of discontinuities that can occur depends not on the number of state variables, which may be very large, but on the number of control variables (also called codimensions), which is generally small. In particular, if the number of control variables is not greater than four, then there are only seven distinct types of catastrophes, and in none of these are more than two state variables involved. The catastrophe is the « jump » from one state or pathway to another. The elementary catastrophes are the seven simplest ways for such a transition to occur.

To represent these families of behaviour, a graph can be used. This graph must have one dimension, or axis, for each control factor that determines a systems behaviour. It must have an additional axis or two to represent the behaviour itself. In the space defined by these dimensions, every possible equilibrium state of a system is represented by a single point, and the points form a smooth line or surface. A continuous change in behaviour appears as a movement within the

line or surface; a discontinuous change appears as a movement that leaves the line or surface. The simplest elementary catastrophe, the fold, has only one control axis and one behaviour axis, and is thus two-dimensional. The most complex, the parabolic umbilic, has four control axes and two behaviour axes, and is thus six-dimensional.

The following table summarises the elementary catastrophes.

Number of control factors	*One behaviour axis*	*Two behaviour axes*
1	fold	-
2	cusp or "Riemann-Hugoniot"	-
3	swallowtail	hyperbolic umbilic - elliptic umbilic
4	butterfly	parabolic umbilic

A more precise definition is needed in order to know what sorts of mathematical operations can be used in the derivations. Two catastrophes are equivalent if one can be transformed to the other by:

(i) a diffeomorphism of the control variables, and

(ii) at each point in the control space a diffeomorphism of the state variables.

The resulting family of state-variable diffeomorphisms must be smooth when considered as a function of the control variables. A *diffeomorphism* is a one-to-one continuous differentiable transformation. The universal unfoldings are defined as follows:

$x^3 + ux$ fold,

$x^4 + ux^2 + vx$ cusp,

$x^5 + ux^3 + vx^2 + wx$ swallowtail,

$x^6 + tx^4 + ux^3 + vx^2 + wx$ butterfly,

$x^3 + y^3 + wxy + ux + vy$ hyperbolic umbilic,

$x^3 - xy^2 + w(x^2 + y^2) + ux + vy$ elliptic umbilic,

$y^4 + x^2y + wx^2 + ty^2 + ux + vy$ parabolic umbilic.

Most of the applications of catastrophe theory are based on the seven elementary catastrophes whose above canonical forms. However, higher order catastrophes can be used as elementary catastrophe theory can be insufficient in some cases.

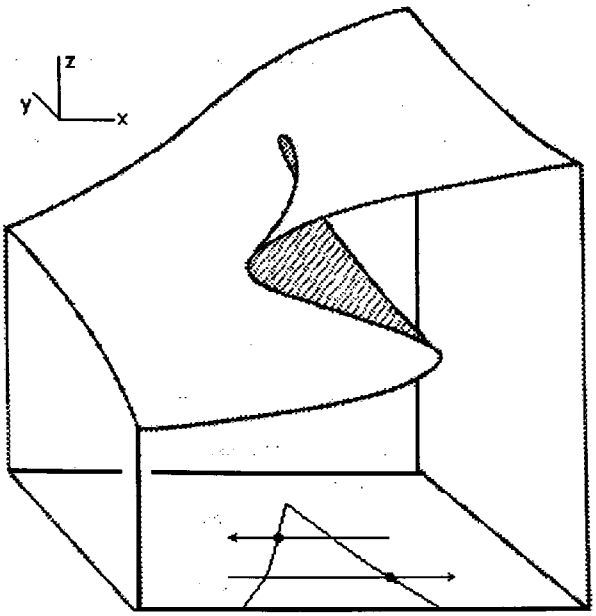

Figure 7-1: Typical cusp-catastrophe surface

7.7.3 Morphologies associated with the seven elementary catastrophes

The fold

The control space is the real line. To the left of the origin there is one stable equilibrium, to the right there are none. If the single control variable is interpreted as spatial, then the fold represents a boundary; if the control variable is interpreted as time then the fold represents beginning or ending.

The cusp

Depending on the choice of convention, the cusp represents a pleat or a fault. If one of the control variables is time then it represents the action of separating (or uniting) or changing.

A typical cusp-catastrophe surface is presented in Figure 7-1.

It is important to remember when using the cusp-catastrophe that generally the shaded part of the manifold is unattainable, and only the upper and lower sheets can represent attainable values. The curve on the surface where the upper and lower sheets fold over into the middle

sheet is called the fold-curve, and the projection of this down into the horizontal plane is called the bifurcation set. Although the fold curve is a smooth curve, the bifurcation set has a sharp point, forming a cusp, and this is the reason for the name cusp-catastrophe. The cusp lines form the main thresholds for sudden behavioural change. The arrows drawn on the bifurcation set indicate the direction of move for values of x and the points at which jumps occur.

The swallowtail

For $u > 0$, the swallowtail divides the v-w plane into two regions, one with a single stable equilibrium, and one with none. For $u < 0$, however, a cusp catastrophe develops within the former region, causing a separation within it. The swallowtail can therefore be interpreted as a split or furrow or, if u represents time, as the action of splitting or tearing.

The butterfly

The interesting case is naturally the one with the butterfly factor, t, negative, for otherwise there is nothing more than a cusp. The butterfly can be interpreted spatially as a pocket, while in the temporal interpretation it corresponds to giving or receiving, or to the filling or emptying of a pocket.

The elliptic umbilic

If all the control variables are spatial, the elliptic umbilic represents a pointed structure such as a spike or a hair; whereas on the temporal interpretation, it represents drilling or filling a hole. It can also represent a liquid jet, but not a stable hydrostatic configuration on account of the cusps; in biology it is possible for the shape to be stabilised by local processes.

The hyperbolic umbilic

Again there is only one stable equilibrium possible. If w is taken as time and interpret its sketches as successive cross sections of a wave, the crest of the wave becomes more and more pointed until it is actually angular ($w = 0$), at which stage it breaks. There is, by the way, some disagreement as to whether or not this account gives a good description of the dramatic

breaking of waves on a beach. The effect can, however, be clearly seen in "symmetric breaking", which often occurs away from the shore.

The hyperbolic umbilic can also be interpreted as an arch, or, taking w as time, as collapsing or engulfing.

The parabolic umbilic

The parabolic umbilic can be interpreted spatially as (for example) a mushroom or a mouth and temporally as the opening or closing of a mouth or as piercing, ejecting or throwing.

7.7.4 Application of catastrophe theory

The applications, in the form of models based on the elementary theory catastrophes (usually the cusp and the butterfly), ranges from natural science to politics, from relatively "solid" to frankly speculative. In thinking about science, a line between two groups of disciplines can be drawn: the exact, "hard" sciences of natural phenomena and the inexact, "soft" sciences of social and cultural phenomena. The first group seems more certain, more down-to-earth, more realistic, because it can offer laws of nature; while the second group has only generalisations. Even some social scientists tacitly share the belief that with time, with better data, and with better mathematical models, their relatively young disciplines will also become like natural science - exact and predictive.

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